BRITISH JOURNAL
OF
OPHTHALMOLOGY

INCORPORATING
THE ROYAL LONDON OPHTHALMIC HOSPITAL REPORTS
THE OPHTHALMIC REVIEW AND THE OPHTHALMOSCOPE

VOL. 42 *SEPTEMBER, 1958* No. 9

EDITORIAL COMMITTEE

Chairman:

SIR STEWART DUKE-ELDER, G.C.V.O.

J. H. DOGGART (*Secretary*)

J. D. MAGOR CARDELL
A. J. B. GOLDSMITH
J. R. HUDSON
STEPHEN J. H. MILLER
E. S. PERKINS
F. A. WILLIAMSON-NOBLE

and the EDITOR of the *British Medical Journal*

LONDON
INSTITUTE OF OPHTHALMOLOGY
JUDD STREET, W.C.1.

Publishing Office
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1.

Ophthalmic Diathermy

The Hamblin "Ophtherm"

FEATURES

Specially designed for retinal detachment operations.

Output adequate for every type of tissue resistance.

Danger of unintentional overdose eliminated.

Hand switch or foot switch control.

Graduated scale enabling conditions to be repeated with exactitude.

Audible beat for timing treatment.

Two models – spark gap or valve.

Hamblin
15 Wigmore St.
London, W.1.

Brit. J. Ophthal. (1958) **42**, 513.

COMMUNICATIONS

SOFRAMYCIN

ITS PENETRATION INTO THE EYE AND ITS EFFECT UPON EXPERIMENTALLY PRODUCED *STAPH. AUREUS* AND *PS. PYOCYANEA* CORNEAL INFECTIONS*

BY

D. AINSLIE AND W. G. HENDERSON

From the Department of Clinical Research and Pathology, Institute of Ophthalmology, London

THE topical application of antibiotics is useful in the treatment of superficial ocular infections, and systemic administration is often effective in overcoming cellulitis of the soft tissues which surround the eye; but it is only by subconjunctival injection that a high concentration of antibiotic can be obtained within the eye. Subconjunctival injection is essential if an attempt is to be made to overcome an intra-ocular infection. Antibiotics which can be administered subconjunctivally are therefore of particular interest to ophthalmologists. To be suitable for subconjunctival injection, an antibiotic must be readily soluble in water and the solution must not be unduly irritating to the tissues.

Only penicillin (Sorsby and Ungar, 1948), streptomycin (Sorsby, Ungar, and Bailey, 1952), and polymyxin (Ainslie and Smith, 1952) have hitherto fulfilled these conditions and all have certain limitations. Penicillin is only slightly irritant when injected, but its range of activity does not cover the Gram-negative bacilli. Many strains of staphylococci are also resistant. Polymyxin is highly effective against Gram-negative bacilli but has no effect upon the coccal organisms. Polymyxin is a moderate tissue irritant and while subconjunctival injection is perfectly safe the injections are very painful. Streptomycin is only slightly irritant and its range of activity covers both Gram-positive cocci and Gram-negative bacilli, but resistant strains of both types of organism develop with ease. Aureomycin, terramycin, chloramphenicol, and erythromycin are of no therapeutic value given subconjunctivally since their water solubility is very low and sufficient concentrations cannot be given. Achromycin is more soluble in water but the solution is irritating when injected.

The appearance, therefore, of soframycin, a new antibiotic with high water solubility and a wide range of activity, seemed to be of considerable interest.

Properties of Soframycin

Soframycin is a white powder highly soluble in water and is naturally produced from the mould *Streptomyces decaris*. It was found that 500 mg. would dissolve

* Received for publication September 7, 1957.

readily in 1 ml. water, and it was equally soluble in mydricaine and xylocaine with adrenaline. It was stable in solution.

Effect of Subconjunctival Injections

A subconjunctival injection of a solution of soframycin was given to six rabbits. The strength of the solution was 500 mg./ml. in every case. Two rabbits received 1·0 ml. (500 mg.), two received 0·50 ml. (250 mg.), and two 0·25 ml. (125 mg.).

Moderate chemosis was present 24 hours later in the case of the two receiving 1 ml. This subsided rapidly and the eyes appeared entirely normal after 4 days. There was no conjunctival necrosis and no corneal oedema. Of the two receiving 0·50 ml., one showed slight chemosis the following day and in the other the conjunctiva was merely reddened at the site of injection. Moderate conjunctival inflammation which rapidly subsided was the only effect noted in the two rabbits receiving 0·25 ml.

These initial observations appeared to suggest that soframycin was almost non-irritant when injected.

Penetration of Soframycin into the Eye after Subconjunctival Injection

Assay.—Since the volumes of aqueous fluids were very small, a capillary tube micromethod was used (Fleming and Smith, 1947; May, Voureka, and Fleming, 1947; Medical Research Council, 1948; Ainslie and Smith, 1952).

Estimates were carried out in duplicate, using the Oxford staphylococcus as the test organism. Unsealed capillaries were incubated in the horizontal position and the end-point was taken as being the last tube which showed no change of colour.

Experiment.—A subconjunctival injection of 250 mg. soframycin was given to one eye of eight rabbits. An aqueous solution of a strength 500 mg./ml. was used in every case. The aqueous humour was withdrawn from each eye 90 minutes later. Aqueous humour was also withdrawn from one eye of each of two rabbits which did not receive soframycin.

The eight aqueous fluids from the rabbits which received the subconjunctival injections all showed levels of soframycin. The amounts, as judged from the degree of inhibition in the tubes, varied from 10 to 40 μg./ml. Aqueous fluids from the two uninjected rabbits produced no inhibition in any tube.

The levels of soframycin found in the aqueous humour in this experiment compared very favourably with the levels of penicillin (Sorsby and Ungar, 1948), streptomycin (Sorsby and others, 1952), and polymyxin (Ainslie and Smith, 1952) in the aqueous humour after subconjunctival injection.

In vitro Sensitivity of Strains of *Pseudomonas pyocyanea*, *Staphylococcus pyogenes*, and "Coliform" Organisms

Ps. pyocyanea.—62 ocular strains of *Ps. pyocyanea*, the majority of which had been collected during a period of years by Dr. Charles Smith and maintained in Robertson's meat medium, were tested. For the tests, stock solutions of soframycin in sterile buffered distilled water (pH 6·8) and stored at 4°C. were used in concentrations of 1,000, 5,000, and 10,000 μg./ml. Strains were sown on nutrient agar plates and the sensitivity determined by the standard filter paper disk technique. The cultures were incubated for 72 hours and the tests were read after

24, 48, and 72 hours. When the plates were examined, strains growing right up to the edge of the disk were recorded as being insensitive. Those showing a definite zone of inhibition, but with a few scattered colonies growing within the zone but not reaching the edge of the test disk, were recorded as showing partial sensitivity. Those showing a completely clear zone were recorded as sensitive. The results of these tests showed that, at 24 hours, six strains of *Ps. pyocyanea* were resistant to 1,000 μg./ml. soframycin, and that after 72 hours the numbers had increased to eleven. Partial sensitivity at 24 hours was shown by fifteen strains and this number increased to 37 strains at 72 hours.

With concentrations of 5,000 μg./ml., there were no completely resistant strains at 24 hours. At 48 and 72 hours, only one strain was completely resistant. Two strains showed partial sensitivity at 24 hours, eight at 48 hours, and eleven at 72 hours.

With concentrations of 10,000 μg./ml., all strains were sensitive at 24 hours. At 48 hours two strains showed partial sensitivity only. At 72 hours three showed partial sensitivity, and two were completely insensitive.

Staphylococci.—250 strains of coagulase-positive staphylococci isolated from routine conjunctival cultures were also tested in a similar fashion. All strains were completely sensitive at 24, 48, and 72 hours with zones of inhibition which were wide and sharply defined. As far as could be judged by using a disk technique, the staphylococcal strains appeared more sensitive than any other organisms tested.

"Coliform" Organisms.—Sixty strains were tested. The results were similar to those obtained with staphylococci. All were completely sensitive to a concentration of 1,000 μg./ml. soframycin, and zones of inhibition were wide and clear cut.

Reports of other *in vitro* studies of soframycin have been few, but are in agreement with our findings. Massenat-Derouche (1954) noted the unusual sensitivity of staphylococci to soframycin, and that the streptococci were also sensitive though rather less so. Lutz and Hofferer (1955) observed that many strains of *B. proteus* were highly sensitive, and found that rather more than 80 per cent. of strains of *Ps. pyocyanea* were sensitive or partially sensitive to soframycin.

Treatment of Experimental Corneal Infections

The effect of soframycin, given subconjunctivally, upon the progress of experimentally-induced corneal infections was determined in a series of experiments.

(*a*) *Staphylococcal Infections.*—Infection was produced by the intracorneal injection of 0·03 ml. of an undiluted 24-hour broth culture of *Staph. aureus.* The right corneae of seventeen rabbits were injected; six were left as controls and eleven received a subconjunctival injection of soframycin within a few minutes of the infecting dose. In each case the strength of the soframycin solution injected was 500 mg./ml. Three rabbits received 500 mg., three 250 mg., and five 125 mg.

In no case where soframycin was given was any sign of infection apparent after 24 hours and no infection developed during the subsequent week. After 24 hours all six controls showed heavy corneal infiltrates varying from 3·5 mm. to 6 mm. in diameter, and the infiltration increased markedly during the next 24 hours.

(*b*) *Ps. pyocyanea Infections.*—Infection was produced by the intracorneal injection of 0·03 ml. of 1:100 dilution of a 24-hour broth culture of *Ps. pyocyanea*. 23 corneae were infected; seven were left as controls and sixteen were given an immediate subconjunctival injection of an aqueous solution of soframycin (strength 500 mg./ml.), eight receiving 125 mg. and eight 250 mg.

Rapidly spreading corneal infection was apparent in all controls after 24 hours, but in nine of the treated cases the corneae were clear after 24 hours and remained so for the following week. In one instance there was a very slight corneal infiltrate apparent at 24 hours which became widespread by the following day. Two corneae remained clear until the third day when a small but spreading infiltrate occurred. In the remaining four, clinical infection was delayed until the fourth day. There was no significant difference between the cases receiving 250 mg. soframycin and those receiving 125 mg. In all cases the subconjunctival injections were well tolerated, there being scarcely any sign of irritation at the site of injection.

Clinical Trials

No extensive clinical trials have as yet been undertaken, but the experimental evidence suggests that soframycin is suitable for clinical use. One patient with a severe hypopyon ulcer has been treated, however. Clinically, the ulcer was of the type due to the pneumococcus, but no organism was grown on culture. This may have been due to the fact that previous treatment with antibacterial ointments had been applied. The infection subsided rapidly after two subconjunctival injections of soframycin 100 mg. dissolved in 0·25 ml. mydricaine given on two successive days.

Discussion

Soframycin is an antibiotic suitable for subconjunctival injection which is exceptionally active against staphylococci. In addition it is effective against many strains of streptococci and Gram-negative bacilli.

Both our *in vitro* and *in vivo* studies indicate the extreme activity of soframycin against the staphylococcus. The results of treatment of corneal infections due to *Ps. pyocyanea* were in accord with the results of the *in vitro* sensitivity tests. Thus, the absence of an absolutely clear zone of inhibition around the test disks, indicating a variable sensivity in the bacterial population of a particular strain, agrees well with the clinical observation that some corneal infections were entirely controlled by a single dose of soframycin, whereas in others the clearance of clinical infection was delayed for a few days.

Summary

(1) Soframycin, an antibiotic active against both Gram-positive cocci and Gram-negative bacilli, is described.

(2) Soframycin is highly soluble in water and was found to be suitable for subconjunctival injection.

(3) Therapeutic levels of the antibiotic were found in the aqueous humour of the rabbit after subconjunctival injection.

(4) All strains of staphylococci tested were highly sensitive to soframycin *in vitro*. Most strains of *Ps. pyocyanea* also showed sensitivity.

(5) Experimental corneal infections due to both *Staphylococcus aureus* and *Ps. pyocyanea* were successfully controlled.

The soframycin used in all experiments was supplied by Roussel Laboratories Ltd., London.

We should like to express our thanks to Prof. Norman Ashton for his helpful advice, and to Miss Margery Hardwick for her technical assistance.

REFERENCES

AINSLIE, D. and SMITH, C. (1952). *Brit. J. Ophthal.*, **36**, 352.
FLEMING, A., and SMITH, C. (1947). *Lancet*, **1**, 401.
LUTZ, A., and HOFFERER, M. J. (1955). *Rev. immunol.*, **19**, 69.
MASSENAT-DEROUCHE, B. (1954). M.D. Thesis, Paris.
MAY, J. R., VOUREKA, A. E., and FLEMING, A. (1947). *Brit. med. J.*, **1**, 627.
MEDICAL RESEARCH COUNCIL (1948). "Report by the Pathological Subcommittee of the Streptomycin in Tuberculosis Trials Committee", *Lancet*, **2**, 862.
SORSBY, A., and UNGAR, J. (1948). *Brit. J. Ophthal.*, **32**, 864.
——, ——, and BAILEY, N. L. (1952). *Brit. med. J.*, **1**, 119.

Brit. J. Ophthal. (1958) **42**, 518.

DENERVATION OF THE LACRIMAL GLAND*

BY

JOHN WHITWELL

Moorfields Hospital and The London Hospital

THE surgical treatment of epiphora is now well established and on the whole satisfactory. A success rate of almost 90 per cent. can be expected for the operation of dacryocystorhinostomy (Stallard, 1950). There still remains a considerable number of cases where the puncta or canaliculi are strictured or absent, where the lacrimal sac is absent or grossly damaged, or where the inner canthus is severely deformed. Every clinic has its cases of chronic epiphora due to dacryocystectomy and to trauma or irradiation of the inner canthus. Although many operations, such as canaliculoplasty, conjunctivo-dacryocystostomy, and canaliculo-rhinostomy have been devised, they are often very time-consuming and the results are far from good.

Several operations have therefore been described for diminishing the secretion of tears. The removal of the palpebral lobe of the lacrimal gland was first performed by de Wecker (1891); the operation was made classical by Axenfeld (1911), and has recently been strongly advocated by Rycroft (1956). The operation is usually successful, but the occasional complication of kerato-conjunctivitis sicca mars the usefulness of this procedure. Keratitis sicca following dacryoadenectomy has been reported by Kalt (1903), Knapp (1929), and Engelking (1928), and I have personally seen two cases. It is probable that the complication is more common than would be supposed from the literature, and that the fear of transforming a wet eye into a dry one accounts for the general reluctance of ophthalmologists to perform this simple operation.

Strebel (1936) attacked the palpebral lobe and the secretory ducts with diathermy. Jameson (1937) divided the lacrimal ductules sub-conjunctivally, an operation which can be graded in extent. It has not been possible to trace any long-term results of this operation. Exposure of the gland to *x* rays has been recommended by several workers (Hensen and Lorey, 1922; Hensen and Schäfer, 1924; Treiser, 1939), and some successful cases were reported. Tikhomirov (1935) described the injection of the palpebral lobe with alcohol.

Patients with epiphora do not suffer constant discomfort and when sitting quietly in a warm room in subdued illumination, have no troublesome watering. Tearing is noticed when in the cold, in a wind, in a stuffy atmosphere such as the cinema, or when concentrating on close work. It is reasonable to suppose, then, that the constant steady level of lacrimal secretion is sufficient to prevent corneal and conjunctival drying, while the reflex excess lacrimation is the main source of disability. The logical treatment would be to abolish this reflex lacrimal secretion.

* Received for publication September 6, 1957.

Nerve Supply to the Lacrimal Gland

The lacrimal nerve, the smallest of the three terminal branches of the ophthalmic division of the trigeminal nerve, enters the orbit through the superior orbital fissure lateral to the annulus of Zinn. The nerve runs forward above the superior margin of the lateral rectus muscle to enter the posterior edge of the gland. Before reaching the gland, the nerve is said to send an anastomotic twig to the zygomatic nerve. It passes through the gland, sending a few filaments to supply the gland substance, and ends by supplying sensory fibres to the skin and conjunctiva.

The facial nerve also supplies the gland. The exact central origin of the fibres is unknown, but they leave the brain in the nervus intermedius and at the geniculate ganglion pass into the greater superficial petrosal nerve. This joins the deep petrosal nerve to form the Vidian nerve, and the fibres thus reach the spheno-palatine ganglion. It is thought that the fibres relay here and that the post-ganglion fibres pass into the zygomatic branch of the maxillary nerve.

Since the detailed course of this nerve in the orbit is described very vaguely in anatomy text-books, several dissections of the human orbit were performed (Fig. 1).

FIG. 1.—Orbit, showing a well-marked zygomatic groove.

In all cases (six subjects), the zygomatic nerve entered the orbit about 5 mm. behind the anterior extremity of the inferior orbital fissure and ran

upwards, outwards, and forwards, usually making a groove in the zygomatic bone (the zygomatic groove). Henceforward, the anatomy is subject to some variation. The groove leads to a foramen which transmits the zygomatico-temporal nerve. Sometimes, the foramen is common to this nerve and the zygomatico-facial nerve, but the latter may enter the orbit as an already separate nerve. At this foramen, the lacrimal branch is given off, penetrates the periosteum, and enters the lateral aspect of the postero-inferior corner of the gland. This point is about 15 mm. behind the lateral orbital margin at the level of Whitnall's tubercle (Fig. 2, opposite).

In one dissection, the zygomatic groove was roofed over with bone and the lacrimal branch appeared to enter the gland directly from the bone (Fig. 3, opposite).

The other common variation is seen when the lacrimal nerve sends an anastomotic branch to join the lacrimal branch of the zygomatic. In these cases, the lacrimal branch penetrates the periosteum earlier and joins with the anastomotic branch to enter the *posterior* aspect of the postero-inferior corner.

In addition, minute orbital twigs are said to pass direct from the sphenopalatine ganglion to the gland through the inferior orbital fissure (Johnston and Whillis, 1942).

The sympathetic supplies the gland from the superior cervical ganglion through the carotid plexus. Fibres reach the gland along the lacrimal artery and along the deep petrosal nerve to follow the same path as the facial nerve fibres.

The role that these nerves play in the control of lacrimation is still not fully understood.

The lacrimal nerve is purely sensory in the reflex lacrimal path. Stimulation of the lacrimal nerve causes copious watering (Czermak, 1860), but stimulation of the distal end of the severed nerve has no effect (Reich, 1873).

Vulpian and Journiac (1879), by experimental methods, and Goldzieher (1894) clinically showed the seventh nerve to be the main secreto-motor supply.

Hutchinson (1876) reported the case of a woman aged 34 years with a right paralysis of the seventh nerve and deafness occurring suddenly 2 days after a confinement; this was associated with "paralysis of the lacrimal gland". In the temporal approach to the Gasserian ganglion, the extradural method carries the risk of damage to the great superficial petrosal nerve and consequent abolition of tearing on that side, while the intradural approach is devoid of this risk (Rowbotham, 1939).

The part that the sympathetic plays is more difficult to assess. Stimulation of the cervical sympathetic in animals has been found to produce copious tearing (Wolferz, 1871; Demtschenko, 1871), while Reich (1873) found variable results and Campos (1897) no effect at all. Duke-Elder (1942) concludes that the sympathetic is responsible for the basis level of tear

FIG. 2.—The lacrimal branch of the zygomatic nerve entering the lacrimal gland. Anteriorly the cut end of the compound ligament is seen at its insertion into Whitnall's tubercle. Also seen are the typical fascial strands uniting the gland to the periosteum.

FIG. 3.—The nerve supply of the lacrimal gland. In this specimen, the zygomatico-temporal nerve is roofed over by bone and the lacrimal branch enters the gland directly from the bone. No anastomosis with the lacrimal nerve was demonstrated.

secretion and the parasympathetic (facial fibres) for the reflex excess lacrimation. Whitnall (1932) gives a similar opinion.

The evidence shows that the parasympathetic secreto-motor fibres from

the seventh nerve are the ones to be divided if the troublesome reflex tearing is to be abolished.

Injection of the Spheno-palatine Ganglion.—Ruskin (1928, 1930) described the posterior palatine approach for the injection of this ganglion with alcohol, and reported a case of epiphora due to previous dacryocystectomy which he treated by this method. This procedure has the merit of speed and simplicity, but the very close proximity of the maxillary nerve and nasal, dental, and palatine branches would appear to render them very liable to injury.

Injection of the Lacrimal Branch of the Zygomatic Nerve.—Several cases of epiphora were treated by a trial injection of 1 per cent. procaine into the region of the secreto-motor nerve. The needle was inserted below the lateral canthal ligament and directed backwards and upwards along the line of the lateral orbital wall. It was hoped that the injection of the nerve with alcohol would be a quick, easy way of treating epiphora. The results of the procaine injections showed a rapid decrease of lacrimation as measured by Schirmer's test, but several patients complained of diplopia caused by lateral rectus involvement. This method of treatment was therefore abandoned.

Denervation of the Lacrimal Gland

This operation was designed to cut the lacrimal branch of the zygomatic nerve as it enters the lacrimal gland (Fig. 4, opposite).

Up to now, general anaesthesia has been employed. The lids are closed by a skin stitch near the centre of the lid margins. An incision about 1 inch long is made with a scalpel from the external canthus laterally, in the line of a skin fold. The incision is deepened to penetrate the orbicularis; the conjunctiva is included in the section and divided with scissors right back into the lateral fornix where it joins the bulbar conjunctiva. Two traction sutures inserted into the cut ends of the external canthus effect a rhomboidal exposure.

The orbital margin is then defined. Attached to Whitnall's tubercle is found a thick fibrous band comprising the lateral canthal ligament, the check ligament of the lateral rectus muscle, and the end of the lateral expansion of the levator palpebrae superioris. This fibrous band is cut as close as possible to the tubercle, immediately allowing a much bigger exposure. The lower pole of the orbital lobe lies immediately above the fibrous band extending downwards behind it, and the next step is to mobilize this part of the gland. It is best commenced by separating the gland from the periorbita in the region of the fronto-zygomatic suture, for here the gland is quite strongly anchored by fascial strands—the "inferior ligament of Schwalbe". The lateral expansion of the levator fascia is then defined and a small malleable copper retractor inserted immediately lateral to it and held by an assistant. In addition, a fine traction suture (000 black) through the lower pole of the gland facilitates the dissection by gentle elevation. The fascial strands of the "inferior ligament" can easily be mistaken for nerve filaments, but no attention should be paid to these until the dissection has reached a point at least half an inch posterior to the orbital margin. Close behind this point, the small neuro-vascular bundle will be seen to pass into the gland. The traction on the gland will give the

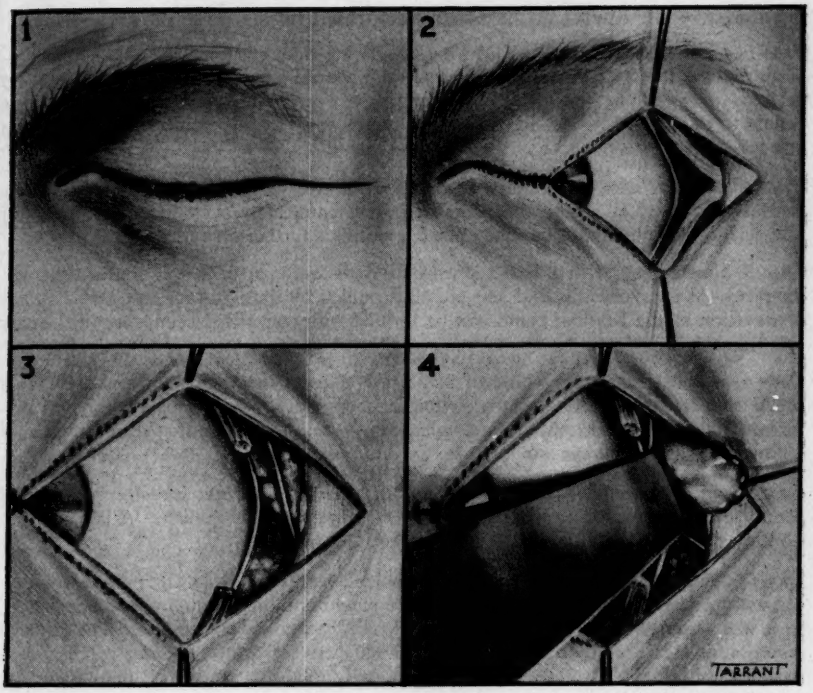


FIG. 4.—Steps in the dissection of the lower pole of the orbital lobe of the lacrimal gland.

course of the nerve a rather characteristic sickle shape as it obliquely penetrates the periosteum (Fig. 2). The portion of the gland which the nerve is entering (the postero-inferior corner) is grasped by a pair of Poirrier's tissue forceps. The nerve is divided as close to the periosteum as possible and the postero-inferior tip of the gland held by the tissue forceps is removed with scissors. If the nerve is not entering the lateral aspect of the gland, it will be seen entering the posterior aspect in conjunction with the anastomotic branch from the lacrimal nerve. Again, the nerve is divided and the tip of the gland excised.

With quiet anaesthesia, haemorrhage is not troublesome and the sucker is not usually needed.

The conjunctiva is closed by three silk sutures (000 black) on a Maddox needle and the skin is sutured with the same material. It has not been found necessary to insert any deep sutures. The wound is covered with tulle gras and an eye pad and a pressure bandage is applied for 48 hours. The lid stitch is then removed and the skin and conjunctival sutures on the fifth day.

Complications.—One case developed a small area of anaesthesia over the region of supply of the zygomatico-temporal nerve, due, no doubt, to an over-enthusiastic attempt to remove as much of the nerve as possible. No symptoms or signs of a sicca syndrome have been observed.

Results.—The operation has been performed on six patients.

Case 1, a male aged 20, had suffered from a watering right eye for 6 months. Investigations showed this to be due to inefficient drainage although no obstruction could be detected on syringing. A denervation of the lacrimal gland was attempted without benefit to the patient. The anatomy of the region was not fully understood at the time and it is likely that the nerve survived the onslaught.

Case 2, a female aged 56, suffered from epiphora after radium treatment to the inner canthus for a rodent ulcer. The canaliculi were completely occluded. An operation was performed but without benefit. She is awaiting a further operation.

Case 3, a male aged 52, had had a left dacryocystectomy performed at another hospital for recurrent dacryocystitis and was greatly troubled by the resultant epiphora. A left denervation of the lacrimal gland was performed with considerable improvement in his symptoms.

Case 4, a female aged 57, who had had a left dacryocystectomy performed 14 years previously, sought advice about the troublesome epiphora. A left denervation was performed and she is now symptom-free, volunteering the information that she can now peel onions without the left eye watering.

Case 5, a female aged 58, had a right epiphora of long standing. Investigation showed complete obstruction of both canaliculi about 3 mm. from the puncta. A left denervation was performed and she is now almost symptom-free.

Case 6, a male aged 63, had had a right facial palsy 3 years previously with partial recovery, but with persistent epiphora. The ducts were patent and the puncta in good apposition, so it was assumed that the muscular apparatus of the sac was inadequate. The lacrimal secretion as measured by Schirmer's test was reduced (see below) but was still sufficient to cause watering. A right denervation was performed and since then the patient has been little troubled.

In five cases, Schirmer's test was performed on the patients before and after the operation, the length of moistened filter paper being recorded in mms, after 5 minutes. In the post-operative test, the length of moistened strips was noted in the usual way after 5 minutes and then the patient was asked to sniff a bottle of strong ammonia. The strips were again noted 1 minute later. This was done to demonstrate the effect on the reflex lacrimal secretion, although it must be remembered that Schirmer's test mainly measures reflex lacrimation owing to the irritating effect of the paper. The findings are recorded in the following Table:

Case No.	*Pre-operative Schirmer's* Test (5 min.)		Post-operative Schirmer's Test			
			5-minute Test		1 minute after Ammonia	
	Right	Left	Right	Left	Right	Left
3	16	16	17	8	24	10
4	18	20	24	9	42	12
6	11	15	5	17	6	28

Conclusion

In cases of epiphora due to blockage of the lacrimal passages, it is the reflex tear secretion that is troublesome. When it is impossible to produce effective drainage, the operation described for cutting the secreto-motor supply to the lacrimal gland may produce considerable relief.

I wish to express my thanks to Mr. A. Lister and Mr. A. G. Leigh for permission to operate upon their patients, and to Dr. V. F. Elbogen for his patient help in translating the German literature.

REFERENCES

AXENFELD, T. (1911). *Klin. Mbl. Augenheilk.*, **49** (1), 345.
CAMPOS (1897). *Arch. Ophtal.*, **17**, 529.
CZERMAK, J. (1860). *In* "Untersuchungen zur Naturlehre des Menschen und der Thiere", ed. J. Moleschott, vol. 7, p. 377. Roth, Giessen. (*Cited by* Tepliachine, 1894.)
DEMTSCHENKO (1871). Diss., St. Petersburg (*cited by* Campos, 1897).
DUKE-ELDER, S. (1942). "Text-book of Ophthalmology", vol. 1, p. 651. Kimpton, London.
——— (1952). *Ibid.*, vol. 5, p. 5209.
ENGELKING, E. (1928). *Klin. Mbl. Augenheilk.*, **81**, 75.
GOLDZIEHER, W. (1894). *Arch. Augenheilk.*, **28**, 7.
HENSEN, H., and LOREY (1922). *Münch. med. Wschr.*, **69**, 1573.
——— and SCHÄFER, H. (1924). *v. Graefes Arch. Ophthal.*, **114**, 126.
HUTCHINSON, J. (1876). *Ophthal. Hosp. Rep.*, **8**, 53.
JAMESON, P. C. (1937). *Arch. Ophthal.* (*Chicago*), **17**, 207.
JOHNSTON, T. B., and WHILLIS, J. (1942). "Gray's Anatomy", 28th ed., p. 1058. Longmans Green, London.
KALT, E. (1903). *In* "Encyclopédie française d'ophtalmologie", ed. F. Lagrange and E. Valude, vol. 1, p. 301, Doin, Paris.
KNAPP. P. (1929). *Klin. Mbl. Augenheilk.*, **82**, 241.
REICH, M. (1873). *v. Graefes Arch. Ophthal.*, **19** (3), 38.
ROWBOTHAM, G. F. (1939). *Brain*, **62**, 364.
RUSKIN, S. L. (1928). *Arch. Otolaryng.* (*Chicago*), **7**, 351.
——— (1930). *Arch. Ophthal.* (*Chicago*), **4**, 208.
RYCROFT, B. W. (1956). *Trans. ophthal. Soc. U.K.*, **76**, 396.
STALLARD, H. B. (1950). "Eye Surgery", 2nd ed., p. 280.
STREBEL, J. (1936). *Klin. Mbl. Augenheilk.*, **97**, 518.
TEPLIACHINE (1894). *Arch. Ophtal.*, **14**, 401.
TIKHOMIROV (1935). *Cited by* Duke-Elder (1952).
TREISER (1939). *Vestn. Oftal.*, **7**, 452.
VULPIAN, A., and JOURNIAC (1879). *C. R. Acad. Sci.* (*Paris*), **89**, 393.
DE WECKER, L. (1891). *Arch. Ophtal.*, **11**, 396.
WHITNALL, S. E. (1932). "The Anatomy of the Human Orbit", 2nd ed., p. 220. Oxford University Press, London.
WOLFERZ (1871). Thesis, Dorpat.

Brit. J. Ophthal. (1958) **42**, 526.

DIVERTICULUM OF THE LACRIMAL SAC*

BY

J. N. ORMROD

From the Corneo-Plastic Unit and Regional Eye Bank, Queen Victoria Hospital, East Grinstead, Sussex

A diverticulum of the lacrimal sac of sufficient size to cause clinical symptoms is a rare occurrence. It is felt that the following example is accordingly worthy of record.

Case Report

A woman aged 33 was admitted to the Unit on February 17, 1957. She had been referred by Mr. W. E. Heath from the Kent County Ophthalmic and Aural Hospital, Maidstone, where she had attended early in 1955 and again in July, 1956. Her complaint was of a swelling in the right lacrimal region which had slowly increased in size since her first attendance in 1955; recently there had been epiphora of increasing severity. The only history of injury that could be obtained was of a blow on the right eyebrow region many years previously and there had been no episodes suggesting inflammation in the lacrimal sac area. There was no associated nasal catarrh and no relevant family history.

Examination.—There was a tense swelling in the region of the right lacrimal sac about 1 cm. in diameter; the overlying skin was freely mobile but there appeared to be an attachment to the deep tissues. The swelling could not be reduced by pressure and syringing of the naso-lacrimal passages revealed fairly easy patency but without alteration in size of the accompanying swelling.

A dacryocystogram was carried out.

X-Ray Report (Dr. W. Campbell):

"Both canaliculi are patent. The lacrimal sac distends with Neohydriol; some trickles through the duct and enters the nose. The base of the sac is deformed and the obstruction is at the neck" (Fig. 1, opposite, and Fig. 2, overleaf).

Operation.—On February 19, 1957, an operation was performed (J.N.O.) under low-pressure anaesthesia (Dr. A. Edrigh). The orbicularis fibres were found to be markedly thinned over a pearly-white cyst which extended above to the medial palpebral ligament and below to the naso-lacrimal duct. The cyst was easily separated from the adjacent structures by blunt dissection; it was removed leaving the lacrimal passages intact. Next day the watering had ceased and the lacrimal passages were freely patent on irrigation.

Pathological Report (Dr. A. Sachs):

(Macroscopical.) "A cyst 1 cm. in diameter filled with caseous-like material."
(Microscopical.) *"The cyst is lined by typical lacrimal sac epithelium.* The walls show the presence of a cellular infiltrate consisting mainly of plasma cells, eosinophils and round cells."
(Diagnosis.) "An infected diverticulum of the lacrimal sac in which the communication with the sac has become shut off."

Discussion

For the diagnosis of a cystic diverticulum arising from the lacrimal sac, it is necessary that the pathological examination of the cyst wall should show it to be identical with the wall of the lacrimal sac, as in the present case.

* Received for publication September 4, 1957.

FIG. 1.—Patency of naso-lacrimal duct with partial obstruction at neck of sac.

Clinical reports of lacrimal diverticula in the literature are few. Michaïl (1932) reviewed the literature and could find only eleven previous reports. He added three new cases of his own: one was small and considered to be of congenital origin, one accompanied an infection of the naso-lacrimal duct by blastomycosis, and one followed injury and chronic inflammation. Spinelli (1937) reported a further case that had developed slowly over a period of 23 years and which was demonstrated by radiological examination after injection of radio-opaque material directly into the cyst. Law (1943) reported a case of recurrent lacrimal abscess with patency of the naso-lacrimal passages in which a lacrimal diverticulum was shown at operation.

Most authors agree that these diverticula may be of congenital, inflammatory or traumatic origin. The embryological researches of Tartuferi (1902) show that an accessory lacrimal sac lying anterolateral to the normal sac and communicating with it at the upper end of the naso-lacrimal duct does occasionally occur; Michaïl's first case is of this nature. Such a diverticulum is initially in communication with the naso-lacrimal duct and its secretions can drain through the duct. Low-grade inflammation or even engorgement of the surrounding plexus of veins could cause this communication to become temporarily or permanently shut off, and the accumulated secretions would set up a low-grade inflammation in the wall of the diverticulum which would further aggravate the condition.

In Spinelli's reported case there was a valve-like communication between the diverticulum and the lacrimal passages allowing radio-opaque material to

FIG. 2.—Deformed base of sac filled with Neohydriol; patency shown by Neohydriol in nasopharynx.

enter the diverticulum from the sac but not in the reverse direction. In a case reported by Franceschetti (1927) the reverse was true and injection of local anaesthetic into the diverticulum passed down the naso-lacrimal duct. In the present case there was no patent communication between the diverticulum and the lacrimal passages.

The present case also showed a chronic inflammation of the walls of the diverticulum, whilst the lacrimal sac exposed at operation appeared normal macroscopically and this normality was further suggested by the ease with which the lacrimal passages were immediately patent following operation. It seems reasonable to postulate that the following sequence of events occurred. First there was a congenital diverticulum of the lacrimal passages; then followed intermittent obstruction of its drainage by vascular engorgement or chronic inflammation, with retention of secretion and increase in size, and pressure on the adjacent lacrimal sac producing epiphora.

Summary

A case of lacrimal sac diverticulum is reported which became large enough to form a visible swelling and which pressed on the normal lacrimal passages producing epiphora. Removal cured the epiphora. It is suggested that the present case was of congenital origin.

I wish to thank Mr. W. E. Heath and Mr. B. W. Rycroft for their permission to publish this case and for their help in its presentation.

REFERENCES

FRANCESCHETTI, A. (1927). *Klin. Mbl. Augenheilk*, **79**, 482.
LAW, F. W. (1943). *Trans. ophthal. Soc. U.K.*, **63**, 295.
MICHAÏL, D. (1932). *Arch. Ophtal.*, **49**, 384.
SPINELLI, F. (1937). *Arch. Ottal.*, **44**, 89.
TARTUFERI (1902). *Ann. Ottal.*, **31**, 545.

Brit. J. Ophthal. (1958) **42**, 529.

STUDIES ON THE CORNEAL AND TRABECULAR ENDOTHELIUM

I. CEMENT SUBSTANCE OF THE CORNEAL ENDOTHELIUM*

BY

F. VRABEC

From the First Eye Clinic, University of Prague, Czechoslovakia

THE corneal endothelium appears to be a very interesting tissue from the morphological as well as physiological point of view. It forms a limiting layer separating the corneal stroma from the aqueous humour, and is therefore said by many authors to have a great physiological importance in the regulation of the water-balance of the corneal stroma. Thus it appears to be of foremost importance for the normal function of the eye, and also continues at the periphery of the cornea as the endothelium of the trabecular meshwork, which seems to be of similar functional importance.

In studying the functional anatomy of the angle of the anterior chamber, it is clear that the function of the trabecular endothelium cannot be understood without better knowledge of the corneal endothelium itself, both tissues being closely related ontogenetically. As the corneal endothelium is easier to study than the trabecular endothelium, this tissue is the subject of the present paper.

The cytology of the corneal endothelium has been studied in many classical papers. One of the as yet unsolved problems is that of the nature of the intercellular substance, in view of the recent work of Jancsó (1955) and McGovern (1955, 1956) on the vascular endothelium and the mesothelium of the peritoneal cavity.

Material and Methods

Fresh corneae of the cat, dog, rabbit, and man were used. Three methods of silver impregnation of the cement substance were tested: the Ranvier classical method, and the new methods of Jancsó (1955) and McGovern (1955, 1956). As the last gave the best results it has been used as a basic method.

Fresh corneae were put into a 0·4 per cent. solution of silver nitrate for about 50 seconds and immediately, without any washing, transferred for 4 minutes into a fresh mixture of 1 vol. 3 per cent. solution of cobalt bromide to 1 vol. 1 per cent. ammonium bromide. Some specimens were then washed in distilled water and fixed, according to

* Received for publication September 30, 1957.

the original McGovern method, by the Carnoy mixture. Other specimens were fixed after the silver impregnation in a 4 per cent. formol solution and cut on a freezing microtome. Both variations proved to be of value; the second being used with greater success to prepare thin sections for photographic records. Some sections were stained in addition by a 1:1,000 solution of toluidine blue. The study of metachromatism by this method was much impaired by the simultaneous intensive metachromatic staining of the corneal stroma. The sections were mounted in Canada balsam or in Apáthy's syrup. The full stereoscopic system gives better evidence of the spatial relations of the substances studied. In some cases, the phase-contrast method and the replica method were of great assistance.

Findings

For the corneal endothelium cells, the description by Kolmer and Lauber (1936) is recommended. Several excellent papers have been published on the subject and the morphology of these cells is well known.

In its simplest form the cement substance of the corneal endothelium corresponds to the classical descriptions. The endothelial elements, mostly hexagonal in shape and of uniform size, are bordered by comparatively narrow, somewhat tortuous lines intensively impregnated with silver. This picture is very similar to that given by staining with Heidenhain's haematoxylin; with the latter the border lines are somewhat narrower than those demonstrated by silver methods. The cement substance forms coarse granules of irregular shape and size. Towards the periphery of the first cat's cornea examined, the border lines grew larger as they approached the corneal margin. The grains of the cement substances appeared swollen and the free inner surfaces of the endothelium cells became narrow in their turn. In the periphery of the cornea—at the limbus region—the granules of cement substance swelled to great balls of a granular substance mostly covering the whole inner surface of the cells. Swollen grains and balls of the cement substance, the colour of which was usually some shade of bluish-grey, took up silver on their surface only. In the central portion of the posterior surface of the cornea, where the surface of the endothelial cells was to a large extent free, as the cement lines were narrow, we got the impression of some other kind of substance covering the remaining free surface of the cells with a thin, smooth layer (Fig. 1, opposite).

This substance did not take up silver, only here and there some fine brownish grains were seen on the surface of the cells. Again, this brownish substance grew towards the periphery of the cornea, and differed quite conspicuously from the bluish-grey cement substance (Fig. 2, opposite).

In some places, the agglomerations of this grey substance were seen to grow to both sides of the originally narrow border lines, which were frequently well preserved in their primary condition. The covering substance on the inner surfaces of the endothelial cells forms a subject of sufficient importance to be treated separately.

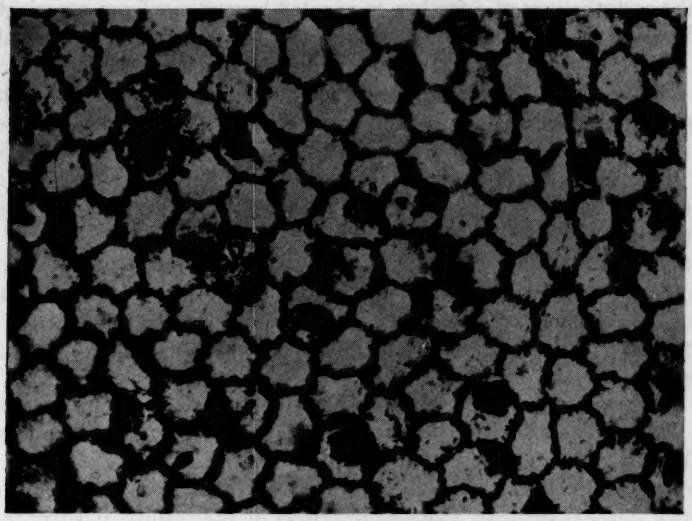


FIG. 1.—Corneal endothelium of the cat; central region of cornea. The cell-boundaries are narrow, and clearly composed of small grains of an argyrophil substance. McGovern's method. ×550.

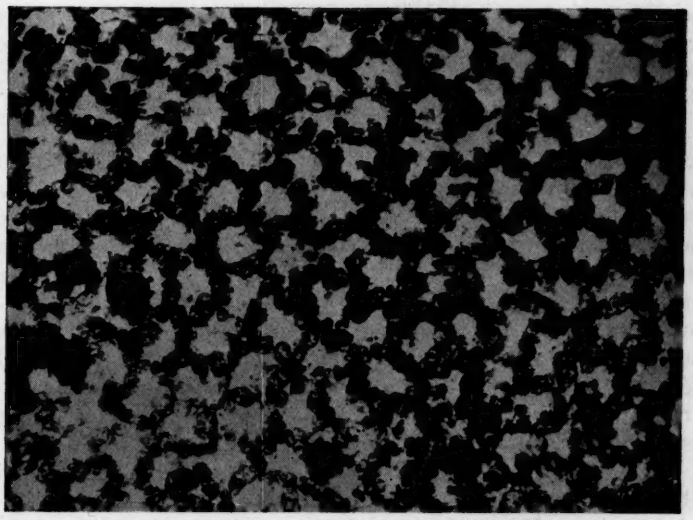


FIG. 2.—More peripheral region of the same cornea as in Fig. 1. The cement substance of the cell-boundaries appears increased and its grains swollen. This material was impregnated immediately after killing the animal by an electric shock. McGovern's method. ×550.

In the endothelium of a freshly enucleated human eye from a patient with an orbital tumour, the cement substance was also enlarged, but this enlargement had taken place throughout the whole posterior surface of the cornea. The vision of the eye was well preserved, but the exposure of the cornea to the air in the lower parts had resulted in a small infiltration at the limbus. Thus it seems possible that the enlargement of the cement substance was due to the slight irritation of the corneal tissue. Irregularities of the border lines were observed (Fig. 3, opposite) as well as the loop formations described by Jancsó and other authors.

In many places doubled and complicated lines were seen, confirming the findings of McGovern, who saw the lines of the cement substance running across the cement surface, not only along the cell boundaries. This observation is perhaps explained by other facts, which will be discussed elsewhere.

At the periphery of the cornea, especially that of man, the endothelial cells often become irregular in shape, elongate in the meridional direction, and form small fan-shaped groups (Fig. 4, opposite).

Similar groups were observed in my previous studies of the relief of the posterior corneal surface. The comparison of the results of silver impregnation with those obtained by the replica method were interesting, as the latter did not demonstrate clearly the granular cement substance and the inner surface of the endothelium cells appeared much smoother. This is further evidence of the existence, in addition to the cement substance, of another kind of amorphous substance covering and smoothing the posterior surface of the endothelial cells as well as the surface of the granular cement substance.

Discussion

The cement substance lining the cell boundaries of the corneal endothelium appears to be very similar to that described by McGovern in blood vessels. The present findings support his descriptions of the behaviour of the cement substance, which is more variable than is generally admitted. This variability of the cement substance cannot be considered as a *post-mortem* change, as it occurred in a certain region of the cornea, whereas at the same time other regions were seen with narrow border lines only. Moreover the human cornea was impregnated immediately after the enucleation. The observations of Jancsó (1955) and other authors also tend to confirm this opinion. While there can be no doubt about this fact, it is questionable whether the part played in this process by the mast cells suggested by McGovern is generally valid. I can find nothing in the literature about the presence of mast cells in the neighbourhood of the corneal endothelium, nor did I find any in a study of the metachromatism of the covering substance. Yet there is certainly some spreading factor which brings about the swelling and perhaps the dissolution of the cement substance by depolymerization, and this substance is probably a

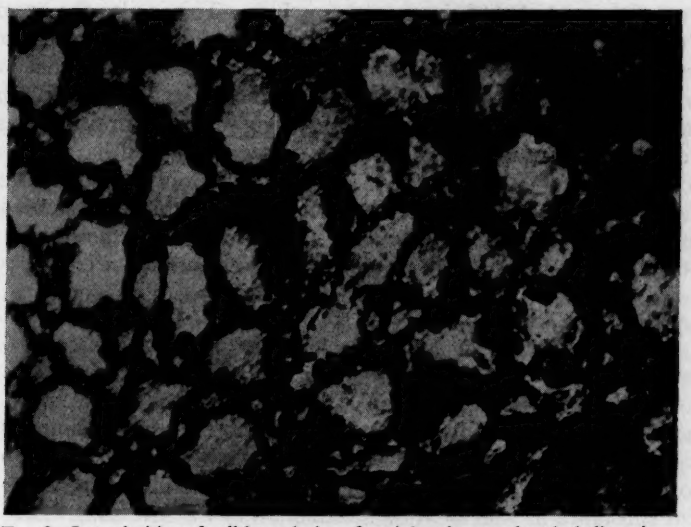


FIG. 3—Irregularities of cell-boundaries of peripheral corneal endothelium in a human cornea. McGovern's method. ×1,000.

FIG. 4.—Human cornea: extreme periphery of corneal endothelium and its transition to the trabecular meshwork. Mosaic pattern of peripheral endothelium. Increased amorphous substance covering surface of endothelium in zone of transition (T) in thin, argyrophil layers. McGovern's method. ×550.

product of the endothelial elements themselves. This is also the opinion of Wolf (1956) in his study of the behaviour and renovation of the cement substance of the vascular endothelium. It seems very probable that various factors are capable of reacting with this substance as well as of modifying the secretion of the endothelial cells. The covering substance appears somewhat different from the cement substance; McGovern and Wolf have also seen a thin covering layer of this kind; that it represents only a modified cement substance (as is supposed by McGovern) appears doubtful to me because of the different behaviour of the two substances. Nevertheless, it seems possible that on some occasions the swollen cement substance could cover the whole free surface of the endothelial cells and—perhaps—unite with the covering substance itself.

Summary

The study of the cement substances of the corneal endothelium revealed some new aspects of this substance and its variability. In the opinion of the author the endothelium probably has an active role in the secretion of the cement substance as well as in the production of the spreading factor which seems to play a part in the dissolution and renovation of the cement substance and its adaptation to various influences.

REFERENCES

JANCSÓ, N. (1955). "Speicherung". Budapest.
KOLMER, W., and LAUBER, H. (1936). "Handbuch der mikroskopische Anatomie", band 3, tome 2. Springer, Berlin.
MCGOVERN, V. J. (1955). *J. Path. Bact.*, **69**, 283.
——— (1956). *Ibid.*, **71**, 1.
VRABEC, F. (1957). *Amer. J. Ophthal.*, **44**, 7.
WOLF, J. (1956). *Čsl. Morfol.*, **4**, 118.

Brit. J. Ophthal. (1958) **42**, 535.

RETINAL VASCULAR MICROMETRY BY THE USE OF A MEASURING OPHTHALMOSCOPE*

BY

MARJORY B. SNODGRASS

The Eye Infirmary, Glasgow

THE eye is the only part of the body in which blood vessels can readily be observed. In disease, retinal blood vessels may show pathological variations in calibre, the severity of which at times reflects the progress of the disease, whether local as in retinitis pigmentosa, or systemic as in spastic hypertension. Spasticity of retinal vessels may show measurable alteration after treatment, in particular during the exhibition of vasodilator drugs. It was felt that a portable instrument sufficiently accurate to measure variations in the calibre of retinal vessels would be of clinical value.

Attempts have previously been made to obtain absolute measurements of delineable, ophthalmoscopically visible retinal structures in the fundus. Numerous methods have been described since Zander (1864) first used a graticule with indirect ophthalmoscopy to measure the calibre of retinal arterioles. Lo Cascio (1922) used a graticule on the heliometer principle, and Lobeck (1934), working independently, produced a more effective heliometer method using the Gullstrand ophthalmoscope. The graticule described by Morgan (1927), which was used by many research workers, was modified by Neame (1936). A further modification, using a prism displacement method, was introduced by Cusick, Benson, and Boothby (1940). Angioscotometry (Solanes, 1947) and modern fundus photography (Lambert, 1934) are two other methods of vascular micrometry.

Some of these methods involve the use of complicated apparatus and others are insufficiently accurate to measure the calibre of the smaller retinal blood vessels. For routine hospital work, it was felt that some adaptation of Morgan's graticule used in conjunction with Keeler's electric measuring ophthalmoscope would prove a practical method.

Apparatus

A graticule was designed with gauges of ten widths ranging from 0·01 mm. to 0·1 mm. (*Fig. 1, overleaf*). These are inserted into the central clear area of a Morgan-type graticule. Each gauge consists of a central black cross bordered by a clear area on each side; the cross and the flanking blank area are of the prescribed width. This graticule was made for me by Messrs. Keeler and fits their

*Received for publication August 20, 1957.

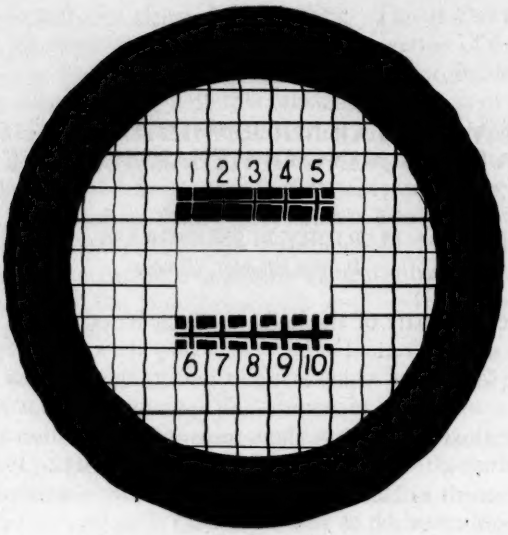


FIG. 1.—Diagram of graticule.

measuring ophthalmoscope. The graticule can be rotated and moved up and down on the ophthalmoscope and, by moving a special focusing button, its image may be focused through the objective on to the fundus (Fig. 2, opposite). The separation between the objective and the graticule is recorded on an illuminated scale in the ophthalmoscope which measures this separation in dioptres when the objective is at the anterior focal point of the eye.

Standardization.—Use was made of the fact that, because of the optical system of the ophthalmoscope, any alteration in the estimated size of a retinal structure due to ametropia, compared with its real size, should remain constant if the graticule is kept in the same dioptric position in the ophthalmoscope. The measurements obtained will only be absolute if the objective of the instrument is at the anterior focal point of the eye. This position is difficult to maintain accurately and, in the following investigation, the ophthalmoscope is held as close to the eye as is comfortably possible in the first examination. Subsequent observations are carried out with the graticule pre-set at the dioptric position recorded at the first examination. Thereafter its image is brought into sharp focus on the fundus by moving the ophthalmoscope nearer to, or further from, the patient's eye, so bringing the instrument to the same distance from the patient's eye as in the first examination. Thus consecutive observations are directly comparable.

Observations

In order to test the accuracy of the instrument, a series of fifteen observations was carried out on young adults showing no clinical evidence of disease of the cardiovascular system. The examinations were carried out in a darkened room. The pupils were dilated by the instillation of one drop of

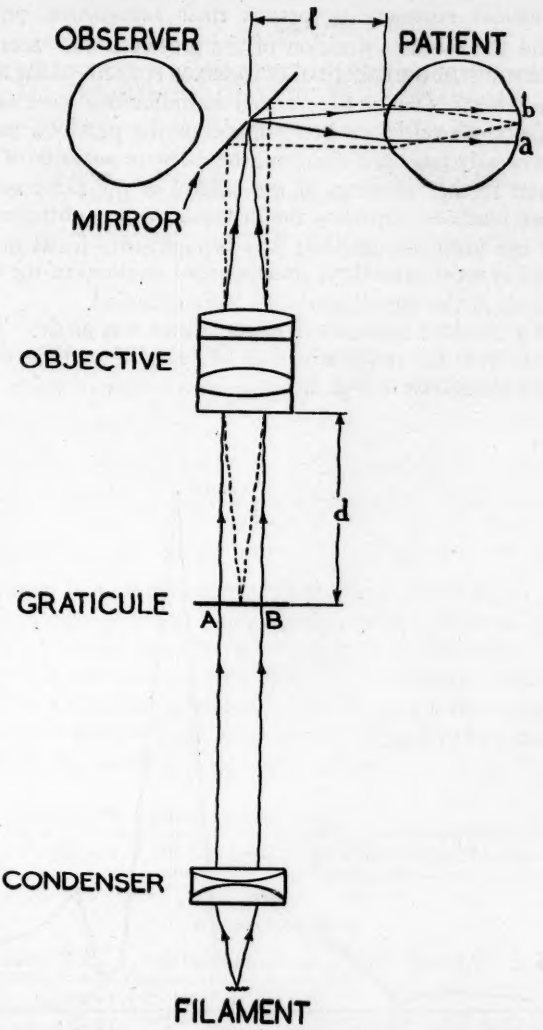


FIG. 2.—Diagram of optical system.

homatropine 2 per cent. and cocaine 1 per cent. and the patient was requested to keep steady fixation on a point of light at 5 m. distance. At the first examination, the ophthalmoscope was held as close as possible to the patient's eye (*i.e.* at about the anterior focal point), and was focused on selected arterioles. The graticule was then brought into accurate focus on the same area. A diagram, including the sections of the retinal vessels measured, was

made of sufficient accuracy to permit their recognition on subsequent occasions, and the dioptric position of the graticule was recorded on this. The estimated width of the calibre of the selected sections of the arterioles was recorded separately. One or two further examinations were carried out on subsequent days, no reference being made to the previous measurements. From the previously recorded diagram, the dioptric position of the graticule was "set" and further readings of the calibre of the same sections of the arterioles were made by adjusting the distance of the ophthalmoscope from the subject's eye until the graticule was brought into focus on the fundus. Thus two, and in most cases three, independent readings of the calibre of the selected sections of the retinal arterioles were obtained.

A series of a hundred such sets of observations was made. The variation of each reading from the arithmetic mean of its set of readings was calculated and the results are shown in Fig. 3.

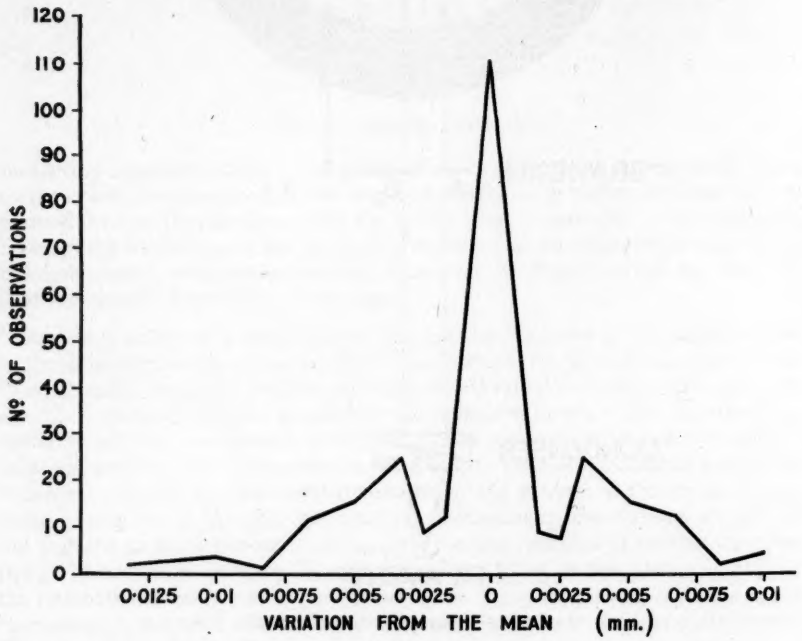


FIG. 3.—Variation of each observation from the mean of its set of observations.

The maximum variation within each set of observations is shown in the Table opposite.

Conclusion

95 per cent. of the readings had a maximum variation of less than the

TABLE

MAXIMUM VARIATION FOR EACH SET OF OBSERVATIONS WITHIN THE SET FROM THE ARITHMETIC MEAN OF THE SET

Maximum Variation as Fractions of Variation in Gauge Widths (0·01 mm.)	Number of Sets
0	42
¼	7
⅓	9
½	15
⅔	19
⅚	3
1	4
1⅓	1

difference between two neighbouring gauge widths (0·01 mm.). If a variation of at least one gauge width is noted, this can be considered significant.

This method of retinal vascular micrometry has a fair degree of accuracy and, although it is time-consuming and involves cooperation from the subject, it should be applicable in clinical work for consecutive observations of the measurement of some retinal structure, and may also be used in research demanding controlled and accurate observations.

This work was assisted by the Spencer Research Trust.

I wish to thank Dr. J. H. Wright, Glasgow Royal Infirmary, for allowing me to examine patients under his care for the purpose of this investigation and Keeler Optical Products Ltd. for their help in making the special graticule and for the use of their blocks in the reproduction of Figs 1 and 2.

REFERENCES

CUSICK, P. L., BENSON, O. O., jr., and BOOTHBY, W. M. (1940). *Proc. Mayo Clin.*, **15**, 500.
LAMBERT, R. K. (1934). *Arch. Ophthal. (Chicago)*, **12**, 868.
LOBECK, E. (1934). *v. Graefes Arch. Ophthal.*, **133**, 152.
LO CASCIO, G. (1922). *Riv. ott. e meccan di precis.*, **2**, S1 (Abs. (1923). *Zbl. ges. Ophthal.*, 9, 189).
MORGAN, O. G. (1927). *Brit. J. Ophthal.*, **11**, 339.
NEAME, H. (1936). *Trans. ophthal. Soc. U.K.*, **56**, 155.
SOLANES, M. P. (1947). *Amer. Heart J.*, **33**, 733.
ZANDER, A. (1864). "The Ophthalmoscope: Its Varieties and its Use", trans. R. B. Carter, p. 101. Hardwicke, London.

Brit. J. Ophthal. (1958) **42**, 540.

OPHTHALMOSCOPIC EXAMINATION*
INCLUDING MEASUREMENT OF SELECTED RETINAL ARTERIOLES IN 15 CASES OF PRE-ECLAMPTIC TOXAEMIA

BY

MARJORY B. SNODGRASS

The Eye Infirmary, Glasgow

OPHTHALMOSCOPIC examination of patients with suspected pre-eclamptic toxaemia may be of help in differentiating between this condition and a pre-existing hypertension of "essential" or other origin; and repeated observations may show changes reflecting the general trend of the patient towards eclampsia or recovery. Descriptions of alterations in the retinal arterioles in pre-eclamptic toxaemia are numerous; these include toxic dilatation in the early stages (Bardsley, 1917), transient spasm of an arteriole (Mylius, 1928), and uniform or irregular spasticity in smaller branches (Selinger, 1937). It was therefore decided to examine the ocular fundi of patients suffering from pre-eclamptic toxaemia during and after the termination of pregnancy, taking particular note of the calibre of retinal arterioles.

Over a period of 7 months all suitable patients who were admitted to the wards of Dr. John Hewitt, Royal Maternity and Women's Hospital, Glasgow, with pre-eclamptic toxaemia were examined; the diagnosis was made on the clinical picture with particular regard to the presence of hypertension, oedema, and albuminuria. Severe cases of pre-eclamptic toxaemia had to be excluded because the proposed examination involved considerable co-operation and concentration from the patient, and the dazzle from the beam of the ophthalmoscope for a period of half to one hour could be sufficient to precipitate an eclamptic convulsion. A total of twenty patients was examined, but in only fifteen of these was it possible to make a complete post-natal examination.

At the first examination the clinical features with particular reference to ocular symptoms were noted and, after an estimation of the refraction, the ocular fundi were examined in detail and the calibre of portions of selected arterioles was measured with a measuring ophthalmoscope according to the method previously described (Snodgrass, 1958). The vessels chosen for measurement were branches of the nasal and temporal arterioles about three or four disc diameters from the optic disc. (Vessels near the periphery were difficult to measure accurately as the image of the measuring grid was distorted in this area.) Where possible a section of an arteriole in each quadrant of both eyes was measured. The same sections were again measured

* Received for publication August 20, 1957.

after the termination of the pregnancy and any change in the fundus picture was noted. If ganglionic blocking agents were used diagnostically, direct observation and measurement of a selected arteriole was carried out during and after completion of the test.

Brief case notes and more detailed ophthalmoscopic descriptions of the fifteen patients are given below. The fundi are described as "healthy" when they fulfil the following criteria:

The media are clear;
The optic discs are clearly defined and pink;
The retinal arterioles are neither too straight nor unduly tortuous, not appearing unduly bright nor pale, and their branches form the expected angle with the parent trunk; at arterio-venous crossings the vein is just visible through the artery and there is no nipping of the vein;
No retinal oedema, haemorrhage, pigmentary upset, or exudate is noted.

The measurements of the retinal arterioles are relative, but in patients with a refractive error of 5 dioptres or less they are almost absolute when the ophthalmoscope is near the anterior focal point as in the method used here. Only Cases 1 and 8 had a refractive error of more than five dioptres. The results are shown in the Table (overleaf).

Case Reports

Case 1, aged 29 years, had previously had six normal pregnancies. During the present pregnancy, occasional mild frontal headaches were complained of and during the 34th week hypertension was noted. The highest blood pressure recorded was 180/110 mm. Hg. There was slight oedema at this time, but no albuminuria. The blood pressure fell slowly with medical treatment and after surgical induction there was spontaneous delivery of a full-term healthy child. The puerperium was uneventful. When the patient was examined 7 months after delivery, there were no ocular symptoms. The blood pressure was 180/85 mm. Hg, and there was no oedema or albuminuria.

Ophthalmoscopic examination at the 36th week of pregnancy showed moderately myopic fundi with healed, diffuse choroidal degeneration. The retinal arterioles appeared healthy apart from sectoral narrowing in the right inferior temporal artery near the disc. On examination 7 months after delivery the sectoral narrowing had disappeared and a significant increase in the measured calibre of the selected portions of arterioles was noted in two out of the seven arterioles measured.

Case 2, aged 27 years, was a primigravida. Oedema and hypertension were noted in the 32nd week of pregnancy. The highest blood pressure recorded was 170/115 mm. Hg. At this time, oedema was marked and there was four parts Esbach of albumen in the urine. A severe throbbing headache, without visual upset, was present. T.E.A.B. and "Vegolysen" tests produced neither a hypotensive response, nor measurable variation in retinal vessel calibre. There was much improvement on medical treatment. Surgical induction at term was followed by forceps delivery of a healthy child. There was post-partum haemorrhage. The blood pressure, oedema, and albuminuria rapidly subsided after delivery and when she was seen 6 months later there were no ocular symptoms, and the blood pressure was 130/85 mm. Hg: there was a trace of albuminuria but no oedema.

Ophthalmoscopic examination at the 34th week of pregnancy showed emmetropic fundi. The retinal arterioles were unduly pale and showed generalized pathological

TABLE

RESULTS IN FIFTEEN CASES

Case	Blood Pressure (mm. Hg)	Oedema	Albuminuria	Measurement in Gauge Widths of Calibre of Arterioles									
				Nasal					Temporal				
1	(*a*) 180/110	TR	–	3·5	5·0	3·5	5·5		5·0	6·5	7·5		
	(*b*) 130/85	–	–	**5·0**	5·5	**4·5**	6·0		5·0	6·5	7·5		
2	(*a*) 170/115	+ +	+ +	3·0	3·5	3·5	3·0		4·0	4·0	4·0	4·0	4·0
	(*b*) 130/85	–	TR	3·5	4·0	4·0	**4·0**		4·5	4·0	4·0	**5·0**	5·0
3	(*a*) 200/120	TR	–	4·5	4·0	4·0	5·0		3·0	4·5	5·5	3·0	
	(*b*) 210/110	–	–	5·0	4·0	4·0	4·5		3·5	4·5	5·0	3·0	
4	(*a*) 190/120	+ +	+ +	4·0	3·0	4·0	3·5	3·5	5·5	5·5	5·0	4·0	
	(*b*) 135/75	–	–	4·0	3·0	4·5	**5·5**	**4·5**	7·0	**7.0**	5.0	**5·0**	
5	(*a*) 180/115	+ +	+ +	5·0	3·5				4·0	6·0			
	(*b*) 135/78	–	TR	5·0	3·5				4·0	6·0			
6	(*a*) 175/110	TR	+	5·0	4·5	3·5	5·0		2·0	3·5	3·5	3·5	3·5
	(*b*) 135/88	–	–	**6·0**	5·0	**5·0**	4·5		2·0	**5·0**	4·0	4·0	**4·5**
7	(*a*) 160/115	+	+ +	3·0	3·5	4·0	3·5		6·0	5·5	6·0	4·0	
	(*b*) 150/100	—	–	**4·0**	4·0	4·5	**4·5**		5·5	5·0	5·5	**5·5**	
8	(*a*) 150/100	TR	–	4·0	4·0				3·0				
	(*b*) 156/55	–	–	4·0	4·0				**4·5**				
9	(*a*) 175/120	+	–	4·0	3·0	2·0	4·0		4·0	2·0	4·0	5·0	
	(*b*) 145/95	–	–	4·0	3·0	**3·0**	4·0		4·0	2·0	4·0	5·0	
10	(*a*) 180/110	TR	TR	3·0	3·0				4·0	5·0			
	(*b*) 160/90	–	–	**4.0**	**4·0**				**5·0**	5·5			
11	(*a*) 170/110	TR	+ +	4·5	3·0	2·5	3·0		4·0	4·0	4·0	3·0	
	(*b*) 120/80	–	TR	5·0	3·5	**3·5**	3·0		4·0	4·0	4·0	3·0	
12	(*a*) 130/85	+	–	4·5	2·5	4·0	4·0		4·0	4·0	5·0	4·0	
	(*b*) 120/75	–	–	4·5	**3·5**	4·0	4·5		**5·0**	4·0	5·0	4·0	
13	(*a*) 180/120	+ +	+ +	4·0	4·0	4·0	4·0		3·0	3·0	4·0	2·5	
	(*b*) 140/90	–	–	4·0	4·0	**5·0**	**5·5**		**4·0**	**4·0**	**5·0**	3·0	
14	(*a*) 168/100	TR	–	5·0	5·0	4·0	5·0		4·0	4·5	2·5	3·5	
	(*b*) 150/95	–	–	4·5	**3·5**	4·0	**3·5**		**3.0**	4·5	**4·0**	3·0	
15	(*a*) 180/115	+ +	+ +	4·0	3·0	2·5	3·0	4·0	4·0	3·0	3·5	4·0	
	(*b*) 130/80	–	TR	4.0	3·0	2·5	**4·0**	4·5	4·0	**5·0**	4·0	**5·0**	

(*a*) Highest blood pressure during pregnancy (mm. Hg).
(*b*) Blood pressure after puerperium (mm. Hg).

narrowing. Patches of retinal oedema were present near the right inferior nasal artery. On examination 6 months after delivery, the fundi appeared healthy. A significant increase in the measured calibre of the selected portions of arterioles was noted in three out of the nine arterioles measured.

Case 3, aged 36 years, had previously had one pregnancy which was terminated by Caesarian section because of the presence of hypertension and placenta praevia. In the present pregnancy, the patient had twice been admitted to hospital because of hypertension, and was admitted again in the 36th week. There was an occasional dull frontal headache, but no visual upset. The highest blood pressure recorded was 200/120 mm. Hg. There was a trace of oedema at this time, but no albuminuria. The T.E.A.B. diagnostic test showed a hypotensive response from 182/105 to 148/88 mm. Hg. Coinciding with the maximum fall in blood pressure, a branch of the left upper nasal artery was observed to dilate from gauge width "4" to "5" for three seconds. The blood pressure settled a little on routine treatment. Forceps delivery at term resulted in the birth of a healthy child. Shortly after this, the blood pressure fell to 170/95 mm. Hg and the oedema and albuminuria disappeared. At a subsequent examination 4 months after delivery, the blood pressure had risen again to 210/110 mm. Hg.

Ophthalmoscopic examination in the 36th week of pregnancy revealed low myopia. The arterioles showed marked calibre variations and slight pallor of the blood columns in the narrower portions. At arterio-venous crossings there was faint obscuration, but no nipping of the veins. Examination 4 months after delivery showed no change in the general fundus picture and no significant change in the calibre measurements.

Case 4, aged 28 years, was a primigravida. Oedema was noted in the 31st week of pregnancy and the following week she was admitted to hospital. There was no history of headache or visual upset. The highest blood pressure recorded was 190/120 mm. Hg. At this time oedema was marked and there was ten parts Esbach of albumen in the urine. Intra-uterine death followed, and mixed accidental haemorrhage and still-birth occurred in the 37th week. The blood pressure returned to normal and the oedema and albuminuria disappeared in the puerperium. The patient was seen post-natally one week, and again 6 months after delivery when there was no oedema or albuminuria and blood pressures of 130/80 and 130/70 mm. Hg were recorded.

Ophthalmoscopic examination at the 35th week of pregnancy showed low hypermetropic astigmatism. The larger arterioles had a broader reflex than usual, but showed no calibre change. There was marked straightening and narrowing of the smaller arterioles and some pallor. The arterio-venous crossings showed slight obscuration with, in one crossing, nipping of the vein. There were three small striate haemorrhages in the right fundus. During a T.E.A.B. diagnostic test the blood pressure fell from 180/105 to 160/95 mm. Hg. Coinciding with the maximum fall in blood pressure, an evanescent, measured, irregular dilatation was observed in a small branch of the right inferior nasal artery from gauge width "1" to "2".

On the first post-natal examination one week after delivery, a soft exudate and a small striate haemorrhage were noted near the left disc and one of the nine arterioles previously measured showed appreciable dilatation. On the second examination 5 months after delivery, spasticity of the small branches of the arterioles had disappeared as also had the haemorrhages. The appearances of the arterio-venous crossings were unchanged. Five of the nine arterioles previously measured showed appreciable dilatation.

Case 5, aged 23 years, was a primigravida. She was admitted in the early months of pregnancy on account of hypertension. She was re-admitted in the 34th week when she suffered from severe frontal headaches. On four occasions she saw flashes of light "like forked lightning" preceding frontal headaches. There were also momentary spots before the eyes "like black dots with haloes round them" which were unrelated to the headaches. The highest blood pressure recorded was 180/115 mm. Hg. Oedema was then marked and there was twenty parts Esbach of albumen in the urine. As there was no improvement in the general condition on medical treatment, Caesarian section was performed in the 37th week of pregnancy. In the puerperium, the blood pressure was 135/80

mm. Hg, oedema had disappeared, and the albuminuria became less than one part Esbach. When she was seen 4 months after delivery, the blood pressure was 135/78 mm. Hg; there was a very faint trace of albuminuria and no visual upset. Headaches were less severe.

Owing to the gravity of the patient's condition in the 36th week of pregnancy, only one eye was examined. It was emmetropic, and pallor and narrowness of some of the very small arterioles were noted, but otherwise the fundus was healthy. Examination 4 months after delivery showed a healthy fundus. Measurement of four arterioles showed no significant alteration in calibre post-natally.

Case 6, aged 37 years, had previously had one normal pregnancy and one miscarriage. In the present pregnancy, the antenatal health was good until the 37th week when she was admitted on account of hypertension. There were no ocular symptoms. The highest recorded blood pressure was 175/110 mm. Hg. Albuminuria then recorded was two parts Esbach and there was a faint trace of oedema. Spontaneous delivery of a healthy premature child followed surgical induction in the 38th week. The puerperium was normal. On examination 2 months after delivery the blood pressure was 135/88 mm. Hg, with no oedema or albuminuria.

Ophthalmoscopic examination in the 37th week of pregnancy showed emmetropic fundi. Narrowing of the right upper temporal artery and definite irregularity of calibre in many small branches of the retinal arterioles were noted. Examination 2 months after delivery showed that the calibre variation had disappeared although the narrow appearance of the right upper temporal artery was still present. Calibre measurement showed a significant dilatation in four of eight arterioles measured post-natally.

Case 7, aged 34 years, had previously had two pregnancies accompanied by pre-eclamptic toxaemia and post-partum eclampsia. During the present pregnancy, the patient had twice been in hospital because of hypertension before being again admitted in the 32nd week of pregnancy when she gave a history of intermittent vomiting and of transient floating black spots in front of her eyes. She had no headache. The highest blood pressure recorded was 160/115 mm. Hg. There was moderate oedema and sixteen parts Esbach of albumen at this time. At the 36th week of pregnancy, labour was surgically induced as there was little response to medical treatment. In the puerperium, the appearance of spots in front of the eyes continued, vomiting ceased, oedema disappeared, the blood pressure was 160/105 mm. Hg, and there was two parts Esbach of albumen. In two examinations, 2 months and 6 months after delivery, there were no symptoms and the blood pressure was 155/105 and 150/100 mm. Hg. Albumen was present in urine in the first examination but absent in the second.

In the 34th week of pregnancy, ophthalmoscopic examination of hypermetropic fundi showed, in the right eye, a choroidal rupture (from a childhood contusion injury). In both eyes, the arterioles were slightly paler in colour than usual, but only in a few small branches was any definite narrowing noted. Marked calibre variation was present in the left nasal artery. There was very slight obscuration of the veins at most of the large arterio-venous crossings. One small striate haemorrhage was seen in the midperiphery of the left fundus. 2 and 6 months after delivery the calibre variation in the arterioles and the haemorrhage had disappeared. The obscuration of the veins at the arterio-venous crossings was unchanged.

Measurement of nine arterioles showed appreciable dilatation in three of them post-natally.

Case 8, aged 36 years, had a history of one miscarriage and two pregnancies complicated by raised blood pressure. She was always subject to migrainous headaches, which were much less frequent during her pregnancies. In the present pregnancy, the patient was

admitted in the seventeenth week on account of a blood pressure of 150/100 mm. Hg. A trace of oedema but no albuminuria was found. She was symptom-free. Her blood pressure settled on rest and she was re-admitted in the 31st week when the blood pressure was 140/90 mm. Hg, and there was slight oedema and a trace of albumen in the urine. A T.E.A.B. diagnostic test carried out in her first admission showed no fall in blood pressure and no change in ophthalmoscopic appearance or measurement of the retinal blood vessels. In the 39th week of pregnancy, she had a spontaneous delivery. In the puerperium the blood pressure was 160/100 mm. Hg and there was no oedema or albumen in the urine. When examined 6 months after delivery, she had frontal headaches, worse on stooping, and occasional dizzy turns. The blood pressure was 165/55 mm. Hg and there was no oedema or albuminuria.

Ophthalmoscopic examination in the 32nd week of pregnancy, showed highly myopic fundi in which fine detail was obscured by cortical lens opacities in the left eye. The blood vessels appeared healthy except for a slight calibre variation in the main arterioles of the left eye. On examination 6 months after delivery, the calibre variation previously noted had disappeared. Measurement, which was difficult on account of the lens opacities in the left eye and the patient's inability to maintain accurate fixation, was carried out in only three vessels, one of which showed appreciable dilatation post-natally.

Case 9, aged 38 years, had previously had seven normal pregnancies. She was admitted in the 35th week of pregnancy on account of raised blood pressure. She complained of occasional mild frontal headaches, but had no visual upset. The highest recorded blood pressure was 175/120 mm. Hg. Oedema was present but there was no albuminuria. The hypertension gradually subsided and in the 39th week, the pregnancy terminated spontaneously. In the puerperium, the blood pressure was 100/70 mm. Hg. There was no oedema or albuminuria. When examined post-natally the blood pressure was 145/95 mm. Hg. There was no oedema or albuminuria.

Ophthalmoscopic examination, in the 36th week of pregnancy, of hypermetropic fundi showed a broadened reflex on the larger retinal arterioles and a few small branches which were pale and very narrow. Light sheathing and irregularity of calibre of the inferior nasal artery of the left eye were present. In the large arterio-venous crossings, there was obscuration of the veins by the arterioles.

Examination 6 weeks after delivery showed no appreciable change in the fundus picture. Measurement of eight arterioles showed dilatation in one of them post-natally.

Case 10, aged 26 years, was a primigravida. She was admitted in the 36th week of pregnancy because of hypertension. She had occasional spots "like midges" in front of the eyes and mild frontal headaches. There was no other visual upset. The highest recorded blood pressure was 180/110 mm. Hg, at which time there was a trace of oedema and half part Esbach of albumen in the urine. A T.E.A.B. test produced no hypotensive response and no ophthalmoscopic change in the calibre of the observed retinal blood vessels. There was little improvement on medical treatment. Surgical induction in the 38th week of pregnancy was followed by forceps delivery of a healthy child. The blood pressure fell to 160/90 mm. Hg, and there was no oedema or albuminuria in the puerperium. When she was examined post-natally there were no symptoms. Blood pressure was 140/80 mm. Hg and there was no oedema or albuminuria.

Ophthalmoscopic examination in the 36th week of pregnancy was carried out in the right eye only owing to the patient's nervousness. There was low myopia. The arterioles were slightly pale and appeared slightly narrow although no variation in calibre was seen. One small area of retinal oedema was noted near the upper temporal artery; 5 months after delivery there was no pallor in the retinal arterioles although the blood vessels still appeared slightly narrow. There was no retinal oedema. Measurement of four arterioles showed dilatation in three of them.

Case 11, aged 19 years, was a primigravida who was admitted in the 37th week of pregnancy on account of the development of hypertension and albuminuria in the previous 2 weeks. On two occasions she saw black spots with haloes round them "like eyes" floating across her field of vision, upwards and to the right. She had no headaches. The highest recorded blood pressure was 170/110 mm. Hg. At this time there was a trace of oedema and twelve parts Esbach of albumen in the urine. There was much improvement in the condition on medical treatment. In the 38th week of pregnancy, a healthy baby was spontaneously delivered. The blood pressure in the puerperium was 120/80 mm. Hg. When she was seen 2 months after delivery there was no oedema and less than one part Esbach of albumen in the urine.

On ophthalmoscopic examination in the 37th week of pregnancy, the eyes were almost emmetropic and the fundi appeared healthy; 2 months after delivery, the fundus appearance was unchanged. Measurement of eight arterioles showed appreciable dilatation in one of them post-natally.

Case 12, aged 40 years, had previously had one normal pregnancy. The present pregnancy was complicated by hyperemesis in the first 3 months. In the 37th week of pregnancy, she was admitted to hospital on account of frontal headaches. The highest recorded blood pressure was 130/85 mm. Hg. Oedema was present but no albuminuria. When she was seen 5 months after delivery, the blood pressure was 120/75 mm. Hg, and there was no oedema or albuminuria. Ophthalmoscopic examination of the fundi in the 37th week of pregnancy showed hypermetropic astigmatism. There was obscuration of the veins at the arterio-venous crossings. Otherwise the fundi appeared healthy. On examination 6 months after delivery, the fundus appearance was unchanged. Measurement of eight retinal arterioles showed appreciable dilatation in two of them post-natally.

Case 13, aged 29 years, had one previous pregnancy which was complicated by hypertension. In the present pregnancy, hyperemesis was present for the first 20 weeks and aching frontal headaches from the 28th week. There was no complaint of visual upset. The patient was admitted in the 32nd week of pregnancy. The highest blood pressure recorded was 180/120 mm. Hg and there was marked oedema with fourteen parts Esbach of albumen in the urine. Caesarian section was performed in this week as the medical condition had not improved. In the puerperium the blood pressure fell to 110/70 mm. Hg and there was no oedema or albuminuria. 6 months after delivery she complained of an occasional frontal headache, her blood pressure was 140/90 mm. Hg, and there was no oedema or albuminuria.

Ophthalmoscopic examination in the 33rd week of pregnancy showed slightly myopic fundi with narrow straight arterioles, some with a slightly pale reflex. There was no irregularity in calibre. Examination of the fundi 6 months after delivery showed disappearance of the narrow straight appearance of the arterioles and of the pale reflex. Measurement of the calibre of eight retinal arterioles showed appreciable dilatation in five of them post-natally.

Case 14, aged 41 years, had previously had eight normal pregnancies and one miscarriage. From the 27th week of the present pregnancy the patient had seen flashing lights "like sheet lightning, though sometimes coloured", which appeared almost daily. At times, when she was reading, black spots floated across the vision from the right upwards. A throbbing "band-like" headache occasionally occurred, associated with excitement and not related to the visual upset; but when the headache was severe, mistiness of vision with occasional flashes of light and buzzing of the ears also occurred. She was admitted in the 36th week of pregnancy. The highest recorded blood pressure was 180/100 mm. Hg. There was a trace of oedema but no albuminuria. Spontaneous delivery of a healthy child followed surgical induction in the 39th week of pregnancy. Blood pressure in the

puerperium was 150/90 mm. Hg. There was no oedema or albuminuria. On examination 7 months after delivery the patient stated that the ocular symptoms had gradually disappeared but oedema was occasionally present. The blood pressure was 150/95 mm. Hg. There was no oedema or albuminuria.

Ophthalmoscopic examination in the 36th week of pregnancy showed low hypermetropic astigmatism. The larger retinal arterioles had an unduly bright reflex and the small branches were narrow and had a pale reflex. Arterio-venous crossings showed nipping of the veins and, in two crossings, kinking of the veins. Small venules around the maculae were more tortuous than normal. Examination 7 months after delivery showed no appreciable change. Post-natal measurement of eight arterioles showed appreciable reduction in the calibre of three and an increase in calibre of one arteriole.

The above findings suggest an underlying essential hypertension complicated by a mild pre-eclamptic toxaemia.

Case 15, aged 27 years, a primigravida, had, for years, been subject to severe headaches accompanied by nausea and lasting about 12 hours. There were no visual phenomena. These headaches remained unchanged throughout the pregnancy. Once in the 25th *week of pregnancy, the patient saw a shower of black spots with golden centres spreading* upwards over the vision and vanishing quickly. The patient was admitted to hospital in *the 30th week when there was marked oedema and ten parts Esbach of albumen in the* urine. The highest recorded blood pressure was 180/115 mm. Hg. The spontaneous *delivery of a healthy child occurred in the 35th week of pregnancy. In the puerperium* the blood pressure fell to 130/80 mm. Hg, the oedema disappeared, and only a trace of albumen was found in the urine. *When she was seen 6 months after delivery, the blood* pressure was 130/80 mm. Hg, there was no oedema, and only a faint trace of albumen was present.

A low degree of hypermetropic astigmatism was present. Ophthalmoscopic examination showed that the larger arterioles were healthy, but that nearly every small branch was markedly narrowed from its commencement, usually irregularly. These branches were too peripheral for accurate measurement of calibre, except in one case. Examination 6 months after delivery showed complete absence of sectorial narrowing in these small arterioles. Measurement of nine arterioles showed appreciable dilatation in three of them, one of which, an obviously spastic vessel, dilated from "3" to "5" gauge widths.

Comment

*The ophthalmoscopic pictures described in this series of cases of pre-*eclamptic toxaemia correspond with the findings of other workers. The actual changes in measurement of the selected retinal arterioles confirm the clinical inference that there is frequently a narrowing of arterioles in this condition. In the present series, this narrowing was occasionally revealed by measurement, although unsuspected from the ophthalmoscopic appearance of the vessels (*e.g.* Case 11).

The most striking result of the investigation was that 37 arterioles (34 per cent.) showed a change in calibre of at least one gauge width and that this change occurred in at least one vessel, in thirteen of the fifteen cases examined. A change of this order was considered significant (Snodgrass, 1958). The changes in calibre were noted with almost equal frequency in the nasal and temporal quadrants, although it has been suggested that nasal arterioles show pathological narrowing before temporal ones (Duke-Elder, 1940).

In Cases 3 and 5, no significant narrowing of measured arterioles was found. In the former, the blood pressure was still raised 4 months after delivery and the presence of slight retinal arteriosclerosis suggested an essential hypertension complicated by toxaemia of pregnancy. In Case 5, narrowness of many arterioles too peripheral for actual measurement was observed, although calibre changes were not found in the four measured vessels. (This patient's general condition did not permit measurement of the usual number of blood vessels.) In Case 14, three arterioles were found to be significantly smaller on the post-natal examination. This may have been due either to dilatation during pre-eclampsia (Bardsley) or more probably to progressive arteriosclerosis accompanying an underlying essential hypertension. As in Case 3, there was a history suggesting this condition.

It is interesting to note that a hypotensive response and measurable dilatation of an arteriole during the administration of a ganglionic blocking agent occurred in two out of five cases (Cases 3 and 4).

It is felt that, in addition to routine ophthalmoscopy in antenatal examinations, regular measurement of the calibre of selected retinal arterioles might be of help in the early diagnosis of pre-eclamptic toxaemia.

This work was assisted by the Spencer Research Trust.

My thanks are due to Dr. J. Hewitt for access to his patients and records and to Dr. J. Marshall for his helpful advice.

REFERENCES

BARDSLEY, P. C. (1917). *Brit. J. Ophthal.*, **1**, 239.
DUKE-ELDER, S. (1940). "Text-book of Ophthalmology", vol. 3, p. 2724. Kimpton, London.
MYLIUS, K. (1928). *Ber. ophthal. Ges. Heidelberg*, **47**, 379.
SELINGER, E. (1937). *Amer. J. Ophthal.*, **20**, 56.
SNODGRASS, M. B. (1958). *Brit. J. Ophthal.*, **42**, 535.

Brit. J. Ophthal. (1958) **42**, 549.

RETROLENTAL FIBROPLASIA IN ASSOCIATION WITH MENTAL DEFECT*

BY

CYRIL E. WILLIAMS

Fountain Hospital, Tooting, London, S.W.17

RETROLENTAL fibroplasia is a major cause of blindness in children. It is usually found in premature children; that is to say, in those with a birth-weight of under 5½ lb (2,500 g.). In the years that followed Terry's original description the incidence of the disease rose steeply and alarmingly. Krause (1955) has estimated that 10,000 children are partly or completely blind from retrolental fibroplasia in the United States of America and that half of all blind children under 7 years of age are blind because of this condition. A vast literature soon grew up around the subject and a great many possible causes for the condition were investigated, but it was not until 1951 that Campbell, in Australia, showed that the condition occurred in premature children who were nursed in high concentrations of oxygen; when she curtailed the administration of oxygen, no further cases occurred. These findings were shortly confirmed everywhere and the role of oxygen in the production of most of the cases of retrolental fibroplasia was established beyond doubt. Thus, in the majority of cases, retrolental fibroplasia is a disease of the eyes induced in premature babies by the administration of excessive amounts of oxygen.

Review of the Literature

Many writers have described a high incidence of mental retardation in association with retrolental fibroplasia. Krause (1946) published an account of eighteen cases of retrolental fibroplasia, of which three had congenital hydrocephalus, one microcephaly, and three more were grossly mentally defective; a further five were probably mentally subnormal, but at that time they were too young for a reliable diagnosis of mental defect. However, 9 years later Krause (1955) published a review of 107 cases: nine were dead, 16 per cent. were of very low mentality, and 20 per cent. were of poor mentality.

Kerr and Scott (1954) found that seven out of twenty cases (35 per cent.) were mentally subnormal, and Forrester (1955), describing the Manchester epidemic of this disease, thought that 20 per cent. were slightly and 10 per cent. grossly retarded. Bjelkhagen (1952) said that fourteen out of 38 cases

*Received for publication September 3, 1957.

found in Sweden were mentally defective; the intelligence in eleven was normal and in the remainder it was uncertain. Potter (1954) reviewed 283 cases of blindness that he had examined for the Royal National Institute for the Blind between October, 1951, and December, 1953; he found 151 cases of retrolental fibroplasia, and of these 26·6 per cent. were retarded and 20·3 per cent. were mentally defective, so that only 53·1 per cent. of his group were considered to be of normal intelligence.

Ineducability and Retrolental Fibroplasia

Through the courtesy of the Chief Education Officer of the Royal National Institute for the Blind, I have been able to review the admissions to and discharges from the Sunshine Homes over the past 10 years. These Sunshine Homes admit about one-third of the blind children in England and Wales for care and early training. The age at admission is usually between 2 and 5 years and if suitable the blind children remain at these homes until they are 7 years old, when they go on to schools for the blind in the normal educational system.

Table I shows that, of 211 children born between 1946 and 1952 who had retrolental fibroplasia and were admitted to the Sunshine Homes, 58 (27·4 per cent.) were ineducable. This group is compared with 294 children blind for reasons other than retrolental fibroplasia of whom 54 (18·2 per cent.) were ineducable. The difference between these figures is significant by the X^2 test (X^2 5·75; $0{\cdot}01 < P < 0{\cdot}02$). From these figures it is evident that

TABLE I

ANALYSIS OF 505 CASES OF BLINDNESS IN CHILDREN SHOWING NUMBERS REGARDED AS INEDUCABLE

Year of Birth	Number of Cases	Cases due to Retrolental Fibroplasia	Ineducable Blind Children				
			(*a*) Blindess due to Retrolental Fibroplasia		(*b*) Blindness due to Other Causes		Total
			No.	Per cent.	No.	Per cent.	
1946	44	5	1	20	7	17·9	8
1947	63	13	5	38·4	12	24	17
1948	66	20	6	30	12	26	18
1949	64	45	10	22·2	6	31·5	16
1950	98	50	21	42	8	16·6	29
1951	101	45	9	20	4	7·1	13
1952	69	33	6	18·1	5	13·8	11
Total	505	211	58	27·4	54	18·2	112

retrolental fibroplasia cannot be regarded as a disease in which the eyes alone are involved.

Table I also shows the tragic and dramatic rise in the incidence of retrolental fibroplasia in children born between 1946 and 1951, together with the gratifying fall in 1952 which has continued in recent years.

Present Investigation

A review of the main causes of blindness in the Ellen Terry Home, Reigate, revealed fourteen cases of retrolental fibroplasia. This unit provides care and training for blind imbeciles, who are admitted from all areas of England and Wales. Table II illustrates the causes of blindness in 51 children who were at the home on November 1, 1956. In addition to these fourteen cases of retrolental fibroplasia, there are three more at the Fountain Hospital, six that have been discharged, and one that has died. It is the purpose of this paper to review these 24 cases and to discuss the relationship between mental retardation and retrolental fibroplasia.

TABLE II

MAIN CAUSES OF BLINDNESS IN 51 CHILDREN AT THE ELLEN TERRY HOME ON NOVEMBER 1, 1956

Optic Atrophy	21
Retrolental Fibroplasia	14
Cataract	10
Corneal Opacity	2
Pseudoglioma	1
Coloboma of Choroid	1
Choroiditis	1
Congenital Absence of Eyes	1
Total	51

Of the 24 cases 23 were premature. A history of being nursed in oxygen tents is available for eighteen of them, in four there is no such history but they were born at a time when it was routine to nurse premature infants in high concentrations of oxygen, and one child received oxygen by nasal catheter and then only at meal times. The case of the one child who was not premature is given briefly below:

A female infant was born in 1944 after a normal labour; her birthweight was 10-lb 6oz (4,680 g.). The pregnancy was an illegitimate one and the mother had previously suffered from syphilis, but at the time of our patient's birth her Wassermann reaction was negative and the child's Wassermann reaction has been negative consistently since birth. There is no history of her having been nursed in an oxygen tent, but she is said to have suffered repeated attacks of bronchitis in infancy. Her left eye was enucleated at the Institute of Ophthalmology when she was 15 months old. Section of the enucleated eye showed cyclitis with a matted retrolental mass involving the totally detached retina and a diagnosis of pseudoglioma was made. The section has recently been examined by Prof. Norman Ashton, Director of the Department of Pathology at the Institute, who states that its histological features are consistent with retrolental fibroplasia.

The aetiology of such cases is in doubt. There seem to be two possibilities. First, the eye condition may be due to a congenital defect, *e.g.* to a persistent

tunica lentis, and may be associated with other abnormalities such as hydrocephalus. Krause (1946) suggested the term encephalo-ophthalmic dysplasia for such cases, but it is interesting to note that one of his infants, who was of normal birthweight and had retrolental fibroplasia, was of good intelligence. Secondly, as suggested by Patz (1954), the eye condition may be due to the fact that in the immediate neonatal period the oxygen saturation of the blood is 90 per cent. whereas *in utero* it is only 50 per cent. This change may affect the immature eye and produce vaso-obliteration which is then followed by outgrowths of new vessels and later by retinal detachment. Numerous cases of retrolental fibroplasia in children of normal birthweight are reported in the literature, perhaps the largest being the series reported by Reese and Stepanik (1954), who saw 20 cases with birthweights between 5-lb (2,270 g.) and 8-lb (3,640 g.), but did not report on their mental level.

Role of Oxygen.—Excessive amounts of oxygen induce retrolental fibroplasia by leading to constriction and perhaps total obliteration of the retinal vessels. When the baby leaves the oxygen tent, this is followed by vasodilatation, outgrowths of new vessels, and fibroblastic proliferation into the vitreous, and subsequently the fibrous tissue contracts to detach the retina. Patz (1954) thought that oxygen led to obliteration of the developing retinal vessels. Ashton, Ward, and Serpell (1954), Bedrossian, Carmichael, and Ritter (1955), and other authors believe that new vessel growth is due to the relative hypoxia which begins on the return of the experimental animal or the premature baby to the normal atmosphere. In other words, Patz thought that O_2 exerted a direct toxic effect on the retinal vasculature, whereas the other workers thought its effects were indirect. Bedrossian and others (1955), Forrester (1955), Szewczyk (1952), and other authors advocated returning a child who developed early signs of the condition to high O_2 concentrations for a further period, after which the concentrations were slowly reduced.

Table III (opposite) shows the duration of O_2 therapy in relation to the degree of mental defect. The numbers here are too small for tests of statistical significance to be applied, but the general impression is that, on the whole, the children most severely affected mentally appear to have been kept in O_2 tents for similar periods to the least affected. The concentration of O_2 may be more important than the length of time in which it is given, but information on concentration was lacking in all our cases.

The duration of stay in hospital tended to be longer for the more severely defective children, the average duration of stay being 68 days. Only four of our cases were diagnosed as having retrolental fibroplasia while in hospital neonatally.

Both Patz (1954) and Ashton and others (1954), who have induced a disorder analogous to retrolental fibroplasia in experimental animals, have sought carefully for evidence of vascular changes in the brain similar to those in the eyes. They were unable to demonstrate that high concentrations of O_2 had any effect on the brains studied. Forrester returned eighteen of

TABLE III

DURATION OF NEONATAL OXYGEN THERAPY AND DEGREE OF VISUAL AND MENTAL DEFECT IN 25* CASES

Case	Days in Oxygen Tent	Degree of Retrolental Fibroplasia	Classification
A. B.	10	V	Idiot
S. B.	28	V	Idiot
J. C.	21	V	Idiot
M. J.	Nil	V	Idiot
N. P.	90	V	Idiot
M. S.	31	V	Idiot
S. C.	Nasal Catheter	V	Imbecile
J. H.	28	V	Imbecile
G. G.	18	V	Imbecile
K. A.	29	V	Imbecile
F. S.	14	V	Imbecile
J. N.	21	V	Imbecile
F. N.	21	V	Imbecile
J. R.	60	V	Feebleminded
M. H.	28	V	Feebleminded
G. C.	25	V	Feebleminded
V. G.	35	V	Feebleminded

* No details of duration of O_2 therapy available in eight cases.

his cases who were developing early signs of the condition to O_2 tents for extended periods but none of them was subsequently mentally retarded. Other authors have failed to find any neural lesions resulting from oxygen poisoning.

Kerr and Scott (1954), however, considered that neural damage in these cases resulted from anoxia and showed that their retrolental fibroplasia group experienced many more so-called "anoxic insults" than a control group of premature infants without retrolental fibroplasia. They felt that the high incidence of neural damage in their cases, together with the retrolental fibroplasia, resulted from anoxia and that high oxygen concentrations increased the anoxia by producing vasoconstriction. Seven of the cases under review suffered neonatal anoxia of marked degree. Ingalls, Tedeschi, and Halpern (1952) produced eye lesions very similar to retrolental fibroplasia in mice by subjecting the mothers to anoxia, and observed that hydrocephalus was seen in significant association with the ocular abnormalities thus induced.

Prematurity and Mental Retardation

King (1950) disputed that there was a special association between retrolental fibroplasia and mental defect and considered that the incidence of backwardness was wholly attributable to the hazards of prematurity. He quoted Hess and Lundeen (1949), who claimed that 10 per cent. of premature

babies suffer mental retardation. This is a line of approach to the problem which needs to be carefully considered.

Reliable studies of the mentality of premature children are relatively few and most of them invite fairly severe criticism. The literature on the subject has been extensively and excellently reviewed by Alm (1953). Ylppo (1919) found that the incidence of imbecility in premature babies was 7·4 per cent., but the expectant mothers and the children in his group were living in Berlin during and after World War I and suffered a high incidence of rickets. Further, the premature babies studied were not a random sample and there were no controls. Many authors (*e.g.* Douglas, 1956) have commented on the pitfalls in studying the results of prematurity. Lack of adequate controls, or controls not suitably matched for age, sex, social class, etc. are frequent shortcomings observed. Peiper (1937) surveyed nineteen articles dealing with the incidence of severe mental disturbance in premature children, and considered that 5·5 per cent. of cases were so affected. Alm studied 999 premature boys born between 1902 and 1921 and matched them with a control group of 1,002 boys of normal birthweight. He found that 4·8 per cent. of the prematures, as against 1·2 per cent. of the controls, were in institutions and that the great majority of these were in institutions for the mentally defective. However, most studies of prematurity include cases weighing under 5½ lb (2,500 g.) at birth, whereas the majority of cases of retrolental fibroplasia are very much lighter than this. Boyd and Hirst (1955), in reviewing 6,926 babies who weighed 4 lb 6 oz (1,950 g.) or less at birth, found that 127 developed retrolental fibroplasia. The incidence of retrolental fibroplasia in children weighing less than 2 lb 4 oz (1,000 g.) was 15·3 per cent., while for those between 3 lb 14 oz (1,730 g.) and 4 lb 6 oz (1,950 g.) the incidence was only 0·2 per cent. That retrolental fibroplasia is associated with extreme prematurity is shown by the Figure (opposite). The birthweights of our series are compared with a control group of 23 children without retrolental fibroplasia, at present in the Fountain Hospital, who weighed less than 5 lb (2,270 g.) at birth. Zacharias, Reynolds, Chisholm, and King (1954) have shown that, in America between 1934 and 1952, there was a three-fold increase in the number of children weighing 4 lb (1,800 g.) or less who survived, and it seems reasonable therefore to postulate that a proportion of these had some degree of neural damage or defect associated with prematurity, and that the association of retrolental fibroplasia in some of them might be purely coincidental.

Douglas (1956), in a detailed study, has been following up all the premature children born in the first week of March, 1946. Out of 676 premature babies, he found that six were educationally subnormal, whereas there were only two so affected in his carefully matched group of controls. The numbers are too small to test for significance. However, he states that premature children resulting from uncomplicated pregnancies have consistently greater handicaps than those from which there is a history of toxaemia, antepartum

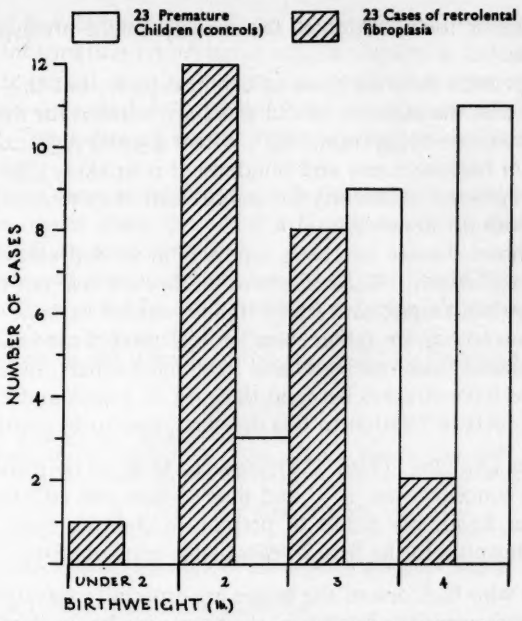


FIGURE.—Birthweights of 46 premature mentally defective children.

haemorrhage, or induced labour. In six of our cases there is a history of antepartum haemorrhage and in three others the mother had toxaemia. In the remaining cases there is no known cause for the prematurity. The report to the Medical Research Council by their conference on retrolental fibroplasia in the United Kingdom (1955) states that the only material factor which was found to have a significantly increased incidence in association with retrolental fibroplasia was antepartum haemorrhage, and, that among the affected babies, there was an excess of those whose mothers had had antepartum haemorrhage of unknown origin. In none of our cases with antepartum haemorrhage was the cause of it ascertained.

In a control group of 23 sighted but defective premature children in the Fountain Hospital, only two had a history of antepartum haemorrhage during their mother's pregnancy, as opposed to six in the retrolental fibroplasia group.

Other Somatic Disorders

Numerous writers have remarked on the high incidence of other somatic disorders found in cases of retrolental fibroplasia. Ingram and Kerr (1954) reported seventeen cases of retrolental fibroplasia in Edinburgh, of whom five had cerebral diplegia. Forrester had seven cases of mono-, hemi-, or di-plegia in his group. Little (1862) remarked on the importance of prematurity in the disease which now bears his name, and Freud (1897) thought

that disturbance of foetal-maternal relationship might predispose children to this affliction.

In our group there were no cases of cerebral palsy, but this may well be due to the fact that the majority of our cases are selected for the Ellen Terry Home on the basis of being trainable. Where a gross physical handicap is added to mental backwardness and blindness it is unlikely that such a child would have progressed sufficiently for a local authority to consider it worth while to refer him for admission.

Congenital heart disease has been reported in several cases; two of our group have heart lesions. Skeletal abnormalities are also not rare, but only one of our cases has a significant lesion (talipes equino varus). One boy has webbed toes, but so had his father; another had double toe nails on one toe. Epilepsy was absent from our series and from most others, though one child was reported to have seizures between the ages of 2 days and 5 months.

Two further facts in relation to this problem need to be mentioned:

(1) To quote Douglas (1956): "Prematures tend to be restless, irritable, and lacking in concentration. . . ." and thus do less well educationally.

On the other hand, his group of premature children spent 3½ times as many days in hospital in the first 2 years as his control group.

(2) Children who lack one of the senses are especially gravely handicapped so that they may appear less intelligent than they are, having lacked appropriate stimulation. Krause (1955) remarks on the fact that the number of children with retrolental fibroplasia in his series, who were considered to be mentally defective, grew smaller with each year. He attributes this to the changing attitude of parents and teachers. Initially he found that blind children were either rejected by their parents at an early age and put into institutions or that the exact opposite happened so that they were over-protected. When better provision was made for the training of both children and their parents, the incidence of backward children fell.

Conclusion

The incidence of mental defect in premature children has been variously estimated as between 4 and 10 per cent. The incidence of severe mental defect in retrolental fibroplasia has varied from 10 to 40 per cent. in different investigations. Due regard has been given to the fact that most cases of retrolental fibroplasia are extremely premature. Despite this there seems to be a higher incidence of mental defect than is to be expected; and further investigations into this problem are needed.

Summary

At least 50 per cent. of children discharged from Sunshine Homes as "ineducable" between 1950 and 1956 suffered from retrolental fibroplasia.

24 cases of retrolental fibroplasia in the Fountain Group of Hospitals are reviewed. Information on neonatal oxygen therapy is lacking in four cases, eighteen were nursed in oxygen tents, one received oxygen by nasal catheter at meal times only, and one did not have oxygen neonatally and was not premature. The degree of mental defect was not related to the duration of oxygen therapy.

There were no cases of cerebral palsy in the series; two cases had congenital heart lesions; in six cases there was a history of antepartum haemorrhage during the mother's pregnancy.

The incidence of mental defect in cases of retrolental fibroplasia appears to be greater than could be explained by the factor of prematurity.

I wish to acknowledge the help given to me by my colleagues at the Fountain Hospital and Mr. Colborne Brown and his staff at the Royal National Institute for the Blind.

REFERENCES

ALM, I. (1953). *Acta paediat.*, **42**, Suppl. 94.
ASHTON, N., WARD, B., and SERPELL, G. (1954). *Brit. J. Ophthal.*, **38**, 397.
BEDROSSIAN, R. H., CARMICHAEL, P., and RITTER, J. A. (1955). *A.M.A. Arch. Ophthal.*, **53**, 514.
BJELKHAGEN, I. (1952). *Acta paediat.*, **41**, 74.
BOYD, J. T., and HIRST, K. M. (1955). *Brit. med. J.*, **2**, 83.
CAMPBELL, K. (1951). *Med. J. Aust.*, **2**, 48.
DOUGLAS, J. W. B. (1956). *Brit. med. J.*, **1**, 1210.
FISHER, R. A. (1944). "Statistical Methods for Research Workers", 9th ed. Oliver and Boyd, Edinburgh.
FORRESTER, R. M. (1955). M.D. Thesis, Cambridge.
FREUD, S. (1897). "Die infantile Cerebrallähmung", *in* "Specielle Pathologie und Therapie", ed. H. Nothnagel, bd 9, tom 3, 2, abt. 2. Hölder, Vienna.
HESS, J. H., and LUNDEEN, E. C. (1949). "The Premature Infant", 2nd ed., p. 322. Lippincott, Philadelphia.
INGALLS, T. H., TEDESCHI, C. G., and HELPERN, M. M. (1952). *Amer. J. Ophthal.*, **35**, 311.
INGRAM, T. T. S., and KERR, J. D. (1954). *Arch. Dis. Childh.*, **29**, 282.
KERR, J. D., and SCOTT, G. I. (1954). *Ibid.*, **29**, 543.
KING, M. J. (1950). *Arch. Ophthal.* (*Chicago*), **43**, 694.
KRAUSE, A. C. (1946). *Ibid.*, **36**, 387.
—— (1955). *A.M.A. Arch. Ophthal.*, **53**, 522.
LITTLE, W. J. (1862). *Trans. obstet. Soc. Lond.*, **3**, 293.
MEDICAL RESEARCH COUNCIL REPORT (1955). *Brit. med. J.*,, **2**, 78.
PATZ, A. (1954). *Amer. J. Ophthal.*, **38**, 291.
PEIPER, (1937). *Quoted by* Alm (1953).
POTTER, C. T. (1954). *Proc. roy. Soc. Med.*, **47**, 715.
REESE, A. B., and STEPANIK, J. (1954). *Amer. J. Ophthal.*, **38**, 308.
SZEWCZYK, T. S. (1952). *Ibid.*, **35**, 301.
YLLPO, (1919). *Quoted by* Alm (1953).
ZACHARIAS, L., REYNOLDS, W. E., CHISHOLM, J. F., and KING, M. J. (1954). *Ibid.*, **38**,, 317.

Brit. J. Ophthal. (1958) **42**, 558.

EXPERIMENTAL DEGENERATION OF THE RETINA*

III. INHIBITORS OF GLYCOLYSIS AND OF RESPIRATION AS INDUCING AGENTS

BY

ARNOLD SORSBY† AND AKIRA NAKAJIMA‡

Royal College of Surgeons of England and Royal Eye Hospital

ONE of the grounds on which disturbance of glycolysis has been assumed to be responsible for experimentally induced degeneration of the retina is the observation recorded by Noell (1951) that injection of sodium iodoacetate abolishes the electric response of the retina much more markedly in mammals than in other species. This finding is suggestive in view of the fact that the mammalian retina is much more dependent on glycolysis than the retina of the lower vertebrates. Furthermore, the high glycolytic activity of the retina raises the possibility that retinal degeneration might arise from interference with this activity; indeed, the action of sodium iodoacetate in inducing experimental degeneration has been ascribed to its possible effect on glycolysis. Since iodoacetate is an outstanding thiol reactor, other such reactors were studied and their effects have been recorded previously (Sorsby, Newhouse, and Lucas, 1957; Lucas, Newhouse, and Davey, 1957). With one exception, none of the thiol reactors used produced any experimental lesions in the rat or rabbit, the exception being bromoacetate, an analogue of iodoacetate, and this gave only a mild lesion in the rabbit and none at all in the rat. The present study was undertaken to test whether inhibitors of glycolysis and respiration—other than thiol reactors—produce retinal damage in the experimental animal *in vivo*. The literature contains several tentative negative results. Thus Karli (1954) failed to obtain degeneration of the retina in the rabbit by the use of sodium fluoride and of phloridzin, and Babel and Ziv (1956) also failed to obtain any results—ophthalmoscopic, electroretinographic, or histological—from the use of fluoride and glyceraldehyde. In the present investigation, a representative series of inhibitors of glycolysis and of respiration was tried in the rat and the rabbit.

Techniques and Agents Used

The procedures in injecting the agents, and the ophthalmoscopic and histological techniques employed in assessing results, were essentially the same as in the previous study. The agents and dosages employed are listed in Table I (opposite). The one innovation introduced was electroretinography carried out on the rabbits. The findings will be recorded separately by one of us (A.N.).

Results

Ophthalmoscopically and histologically none of the agents produced any changes in the retina in the rat or rabbit. As most of these agents are largely

* Received for publication September 18, 1957.

† Wernher Group for Research in Ophthalmological Genetics, Medical Research Council.

‡ Department of Ophthalmology, Jutendo University, Tokyo. Working in London 1956–57 as a British Council Scholar.

TABLE I

INHIBITORS OF CARBOHYDRATE METABOLISM ADMINISTERED INTRAVENOUSLY TO RATS AND RABBITS

	Substance	Rats		Rabbits		
		No. of Animals Treated (a single dose)	Dose* (mg./kg.)	No. of *Animals* Treated	Dose* (mg./kg.)	No. of Full *Doses* Given
Mainly or Exclusively Inhibitors of Respiration	Sodium cyanide ..	—	—	1	0·5	1
	Sodium oxalate ..	2	75	2	50	2†‡
	Sodium malonate	*3 (a)*	*1,500*	*1*	*700*	*2†*
	Sodium maleate ..	2	3,660*	1	250	1†
	Sodium fluoracetate	1	2·0	1	0·25	2†‡
	Phenosafranin ..	1	10	4	5·0–6·0	3; 3; 3; 2‡
	Congo red ..	2	200	1	250	1†
	Triiodobenzoic acid	*2*	*75**	*1*	*200**	*1*
	Malononitrile ..	—	—	2	10	1; 2†
	Sodium azide ..	2	20	1	12·5	2†‡
Mainly or Exclusively Inhibitors of Glycolysis	DL-Glyceraldyehde	1	117*	1	300	1†
	Methyl glyoxal ..	2	100	1	50	3
	Sodium fluoride ..	2	30	1	65	2‡
	Nicotine	2 (*b*)	0·5–1·0	1	3·0	3

* Maximum tolerated dose, except that for the three agents carrying a * sign; the dose was limited by solubility and the maximum tolerated dose could not be established.

† In addition to the maximum tolerated dose, one or more submaximal doses were administered, generally before the maximum dose.

‡ Found dead overnight after the last injection.

(*a*) One further animal received 2,500 mg./kg. and survived for 30 minutes; histologically negative.

(*b*) Two further animals received 2 mg., and two animals 4 mg. subcutaneously; histologically negative.

inhibitors of either glycolysis or of respiration, these negative results raised the possibility that retinal damage might be produced if inhibitors of both functions were administered simultaneously. For this purpose the combined use of two such inhibitors was tried as shown in Table II (overleaf).

It should be noted that some of these agents are known to have other effects too. The doses used were generally more than half the dose used for each agent separately and were mixed together just before injection. It will be seen that the combination of a respiratory inhibitor like *p*-chloromercuribenzoate with fluoride and mapharside—both known inhibitors of glycolysis—gave no retinal damage. Similarly, respiratory inhibitors like malononitrile and cyanide combined with inhibitors of glycolysis like fluoride, mapharside, and glyceraldehyde, though given to the limit of tolerance, gave no results, except that a marked retinal degeneration set in when the combination of cyanide and fluoride was used. At first with small doses of these agents (0·25 mg. and 35 mg./kg. respectively) there was no ophthalmoscopic lesion, but a localized reaction was observed when the same animal received a larger dose (0·60 mg. and 45 mg./kg.). A fairly similar dose administered as a single injection in a further rabbit gave the fundus appearances shown in Fig. 1 and the histological changes shown in Fig. 2 (overleaf).

Ophthalmoscopically, the course and appearance of this experimental degeneration were very similar to those produced by sodium iodate. The effect, however, was not always obtained. These substances—generally in a dose of 0·5 mg. cyanide and 50 mg. fluoride—given to 30 more rabbits produced an immediate mortality of eight and only three positive results amongst the 22 survivors. Fifteen of the nineteen unresponsive rabbits produced no further positive result from two or three repeated injections. In all, there were, therefore, five positive results in a series of 24 survivors.

TABLE II

SIMULTANEOUS INTRAVENOUS INJECTION INTO THE RABBIT OF INHIBITORS OF GLYCOLYSIS AND OF RESPIRATION

Agents Used	No. of Animals	Doses (mg./kg.)	No. of Days Observed	Remarks
Sodium fluoride and p-chloromercuribenzoate	1	45 15	4 (*a*)	No retinal damage.
Mapharside and p-chloromercuribenzoate	1	1·5 15	15	No retinal damage.
Sodium fluoride and Malononitrile	2	40 5	3 (*b*); 4	No retinal damage.
Mapharside and Sodium cyanide	1	1·5 0·65	7 (*b*)	No retinal damage.
DL-glyceraldehyde and Sodium cyanide	1	210 0·65	5	No retinal damage.
Sodium fluoride and Sodium cyanide	1	35 0·25	14	No retinal damage after the first dose. A second combined dose of 0·6 and 45 mg./kg. respectively gave a retinal reaction within 3 days; this was rather more localized than the reaction obtained with a single combined dose of 0·50 and 50 mg./kg. respectively.
Sodium fluoride and Sodium cyanide	1	50 0·50	18	
Sodium fluoride and Sodium cyanide	22	37–65 0·37–0·5	4–28	Retinal damage from one injection in three rabbits.
Sodium fluoride and Sodium azide	1	60 8	8	Dose repeated and animal observed for 4 days more; no retinal damage.
Sodium azide and Malononitrile	1	10 10	8	Dose repeated and animal observed for 4 days more; no retinal damage.

(*a*) Destroyed because of paralysis of hind-legs. (*b*) Found dead.

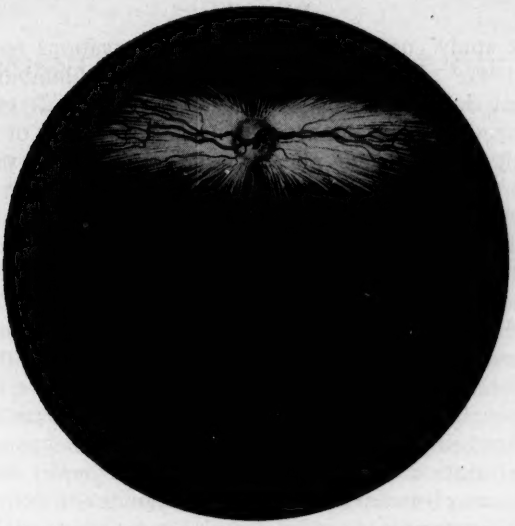


FIG. 1.—Fundus of rabbit 18 days after a single intravenous injection of 0·5 mg./kg. sodium cyanide simultaneously with 50 mg./kg. sodium fluoride. Below a zone of oedema or coagulation necrosis abutting on the disc, there is a wide zone of extensive pigmentary degeneration, which began to develop 3 days after the injection.

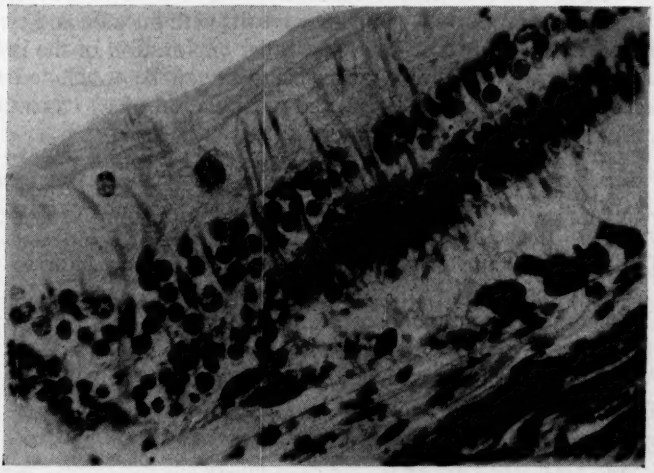


FIG. 2.—Section of the retina shown in Fig. 1. Note the extensive breaking up of the cells of the pigmented epithelium and of the visual cells, most marked to the left. A chorio-retinal adhesion with invasion of pigment is present at a break in the outer limiting membrane. The section is of retina near the disc.

Two single attempts to produce retinal degeneration by the use of azide together with fluoride, or with malononitrile were both negative.

Discussion

The present study confirms the scattered observations recorded in the literature that the administration of carbohydrate inhibitors does not produce retinal damage in the experimental animal. It carries matters further in bringing out that neither inhibitors of glycolysis or of respiration give any result. The Pasteur phenomenon suggested the possibility that the failure of these specific inhibitors might be due to the fact that the remaining carbohydrate system would act for both itself and the system excluded by the inhibitor. The results recorded with the combined use of cyanide and fluoride lend some support to this assumption, but the negative results with other similar combinations raise considerable difficulties. For the moment it is of some significance that experimental degeneration of the retina has been achieved by a procedure deduced from the established fact that the retina is highly dependent on glycolysis and respiration. The possibility arises that sodium iodoacetate induces degeneration of the retina by virtue of its being an inhibitor of both respiration and glycolysis—a reading not altogether supported by electroretinography which shows a different response as between iodoacetate and cyanide and fluoride combined. Moreover, this assumption would not explain why ethyl iodoacetate, which is almost as effective as sodium iodoacetate as an inhibitor of respiration and of glycolysis, fails to produce retinal degeneration; nor would it explain why sodium iodate which does not inhibit either function, readily produces a lesion. The low proportion of positive results with fluoride and cyanide in combination does in any case call for a fuller exploration of the individual inhibitors of glycolysis and respiration before it can be concluded that the effect recorded here is indeed due to the combination of two agents.

Summary

(1) A series of inhibitors of respiration and of glycolysis was used intravenously in rats and rabbits in sublethal doses without producing any degeneration of the retina.

(2) The combined use of sodium cyanide and sodium fluoride—typical inhibitors of respiration and of glycolysis respectively—produced a marked retinal degeneration ophthalmoscopically and histologically in five out of 24 animals treated.

(3) As yet other similar combinations have given no result; the theoretical implications are indicated.

We are indebted to Dr. D. R. Lucas for help with this work, and especially for the histological reports. To Mr. J. P. Newhouse we are obliged for guidance on the selection of biochemical reagents. We are indebted to Mr. R. Harding for technical assistance.

REFERENCES

BABEL, J., and ZIV, B. (1956). *Ophthalmologica (Basel)*, **132**, 65.
KARLI, P. (1954). *Ibid.*, **128**, 137.
LUCAS, D. R., NEWHOUSE, J. P., and DAVEY, J. B. (1957). *Brit. J. Ophthal.*, **41**, 313.
NOELL, W. K. (1951). *J. comp. Physiol.*, **37**, 283.
SORSBY, A., NEWHOUSE, J. P., and LUCAS, D. R. (1957). *Brit. J. Ophthal.*, **41**, 309.

Brit. J. Ophthal. (1958) **42**, 563.

EXPERIMENTAL DEGENERATION OF THE RETINA

IV. DIAMINODIPHENOXYALKANES AS INDUCING AGENTS*

BY

ARNOLD SORSBY† AND AKIRA NAKAJIMA‡

Royal College of Surgeons of England and Royal Eye Hospital

RAISON and Standen (1954, 1955) and Collins (1954) have independently drawn attention to the high schistosomicidal activity of the diaminodiphenoxyalkanes. Clinical trials with one of these agents, 1:7 di(*p*-dimethylaminophenoxy) heptane, has apparently been carried out and has given retinal complications (Grant, 1956, 1958). Experimental evidence that the allied 1:5 di(*p*- aminophenoxy) pentane produces retinal lesions has been given by Edge, Mason, Wien, and Ashton (1956), who recorded that the monkey, dog, and cat (when given 100–400 mg./kg. by mouth or by subcutaneous injection, or 25–50 mg./kg. intravenously) developed fundus changes simulating retinitis pigmentosa. They could not obtain any lesions in the mouse, rat, guinea-pig, rabbit, or ferret, treated with single oral doses up to 400 mg./kg. (about two-thirds the mean lethal dose in the mouse). An account of the histological changes induced by this agent in the cat retina has been given by Ashton (1957). In a study on the toxicity of the alkane derivatives, Goodwin, Richards, and Udall (1957) have stressed the retinotoxic effects of these agents when administered by mouth or by subcutaneous injection. Large and repeated doses given by mouth had no apparent effect on the eyes of mice, rats, or guinea-pigs, but gave ready results in the cat, especially with primary and secondary amines; the effects of tertiary amines seemed less constant. Apart from histological studies, they used the Zewi technique of assessing resynthesis of rhodopsin to determine retinal damage; here, too, they found the primary amines the most and the tertiary the least toxic.

The present study was undertaken to test a fairly wide range of diaminodiphenoxyalkanes, the rabbit being used as the test animal and the agents being injected intravenously.

Methods and Agents Used

Seven primary amines in the diphenoxyalkane series, two secondary methyl amines, seven tertiary methyl amines, and two tertiary ethyl amines were used. In all these compounds the amine was in the *para* position. Two further agents were also employed, one being a tertiary methyl amine in the *ortho* position and the other a tertiary hydroxyethyl amine in the *para* position. The structural relationship of these agents and the doses employed are shown in Table I (overleaf), which

* Received for publication September 16, 1957.

† Wernher Group for Research in Ophthalmological Genetics. (Medical Research Council).
‡ Department of Ophthalmology, Jutendo University, Tokyo. Working in London 1956–57 as a British Council Scholar.

also shows that most animals received a single injection of the agent, though some were given several injections, generally to step up the dose. In a few cases, injections were given in two or more divided doses because of the acute toxicity of the agent. The tolerated dose of the different agents varied rather widely, as did the physical properties. Thus one particular agent, 1:8 di(*p*-aminophenoxy) octane, was barely soluble even in its hydrochloride salt. As for the acute toxicity of the agents, the best tolerated were the primary amines, whilst most of the remaining

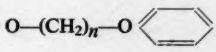
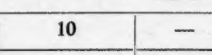
TABLE I

DOSAGE AND EFFECTS OF DIAMINODIPHENOXYALKANES

Where $n=$	No. of Animals	Dosage: Single Intravenous Injections unless Otherwise Indicated (mg./kg.)	Acute Toxicity	Duration of Observation (days)	Retinal Damage	Lethal Doses (mg./kg.) where established
Primary amines: NH_2 $O-(CH_2)_n-O$ NH_2						
2	1	50	Slight	14	—	120
	1	100	Moderate	27	—	
3	1	50	Slight	13	+ +	
	1	5	„	16	?±	
5	3	40	Slight	21; 2; 5	+ +	$\bar{c}$ 100
	1	60	Slight	40	+ +	
	1	5	„	16	+	
6	1	40	Moderate	17	+ +	$\bar{c}$ 40
	1	25	Slight	3	+ +	
	1	5	Slight	10	+ +	
	1	0·3	„	32	?±	
7	1	100	Slight	7	+ +	
	1	60	Slight	21	+ +	
	1	40	Slight	3	+ +	
	1	10	Slight	10	+ +	
	1	5	Slight	10	+ +	
8	1	10	Slight	6	+ +	14
	1	3	Slight	17	+ +	
	1	1	„	5	–	
9	1	56	Severe	2	+ +	$\bar{c}$ 60
	1	36	Slight	17	+ +	
	1	8	Slight	7	+ +	
	1	4	„	4	+ +	

contin.

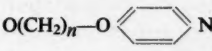
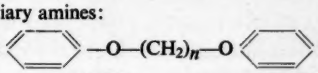
TABLE I—*continued*

Where $n=$	No. of Animals	Dosage: Single Intravenous Injections unless Otherwise Indicated (mg./kg.)	Acute Toxicity	Duration of Observation (days)	Retinal Damage	Lethal Doses (mg./kg.) where established
Secondary methyl amines: CH_3HN $O-(CH_2)_n-O$  $NHCH_3$						
5	1	50; 50; 63; 90	Marked[1]	29	—	
	1	75	Marked	30	—	
7	1	30; 50; 60	Marked	10	—	110
	1	75	Marked	25	+	
Tertiary methyl amines: $N(CH_3)_2$ $O-(CH_2)_n-O$  $N(CH_3)_2$						
4	1	20	Marked	10	—	40
5	1	100; 80; 100	Marked	58	—	160
6	1	16; 25	Slight	30	—	
7	1	160	Severe[2]	2	—	?<50
	1	28*; 36	Slight	38	+	
8	1	4·5; 13*	Slight	11	—	<10
9	1	6·6*; 23*; 23*	Slight	52	?±	<10
10	1	8; 15*	Slight	33	—	

[1] Paralysis of hind legs with 90 mg./kg.

[2] This rabbit receiving 160 mg./kg. survived, but had to be destroyed 2 days later because of paralysis of hind legs.

* Divided over two or more doses, all injected within an hour.

Tertiary ethyl amines: $N(C_2H_5)_2$ $O(CH_2)_n-O$  $N(C_2H_5)_2$						
4	1	25; 43	Severe	4	—	
7	1	200	Slight	28	+	350
	1	250	Slight	5	—	
	1	300	Severe	10	—	
Other tertiary amines: Methyl amine in *ortho* position:  $-O-(CH_2)_n-O$ $N(CH_2)_2$ $N(CH_2)_2$						
5	1	33	Severe	34	—	40

contin.

TABLE I—*continued*

Where $n=$	No. of Animals	Dosage: Single Intravenous Injections unless Otherwise Indicated (mg./kg.)	Acute Toxicity	Duration of Observation (days)	Retinal Damage	Lethal Doses (mg./kg.) where established
Hydroxyethylamine: $(HOCH_2CH_2)_2N$ $O(CH_2)_nO$ $N(CH_2CH_2OH)_2$						
7	*1*	*200*	Slight	28	—	
	1	150	Slight	27	—	

agents, especially the secondary methyl amines and the tertiary ethyl amines, were particularly difficult to use, as convulsions and paralysis of the hind legs were readily precipitated. The experimental and ophthalmoscopic techniques employed were essentially those recorded in the previous studies on inducing agents of experimental degeneration of the retina (Sorsby, Newhouse, and Lucas, 1957; Sorsby and Nakajima, 1958). The material was fixed in acid Zenker's solution and embedded in ester wax after dehydration in 2 ethoxy-ethanol (Chesterman and Leach, 1956). Electroretinographic records are reported separately by one of us (A.N.).

Results

The results obtained with these twenty agents show a fairly simple pattern. Of the seven primary amines, six gave a marked and rapidly developing retinal lesion when the agent was given in a single intravenous dose. The seventh primary amine used—the one with the lowest carbon chain—gave an indefinite result ophthalmoscopically and histologically. Of the remaining thirteen agents, all but three proved negative, and the three positive results were not readily obtained. As will be seen from Table I, the positive result obtained with the secondary methyl amine with seven carbon chains was reached with a sub-lethal dose, repeated smaller doses giving no effect. Likewise, the positive result obtained with one of the tertiary ethyl amines was balanced by negative results in two animals receiving higher doses but observed over a shorter period. The positive result obtained with the tertiary methyl amine was not marked. The striking findings in this series were therefore confined to the primary amines, the one with two carbon chains excluded.

The ophthalmoscopic picture was fairly constant with the six primary amines that gave a positive result, and was very similar to that observed with iodate and iodoacetate. Within 2–3 days there was loss of translucency of the retina, showing itself ophthalmoscopically by an appearance simulating oedema of the retina; some narrowing of the arteries was common and pigmentary proliferation began to set in within 5 days and tended to progress

for the next 2–3 weeks. The fully developed picture was generally present within 21 days. Histologically the visual cells and pigmented epithelium were most affected. Figs 1 and 2 are fairly typical of these appearances. In contrast, the positive results obtained with one of the secondary amines and two of the tertiary amines were ophthalmoscopically slow in onset, taking some 3 weeks to show anything definite, whilst histologically the lesion was mild.

FIG. 1.—Rabbit retina 21 days after injection of 60 mg./kg. 1:7 di(*p*-aminophenoxy) heptane. H and E ×400.

Note total disappearance of visual cells and disruption of cells of pigment epithelium. There is also considerable invasion of pigment into the inner layers of the retina.

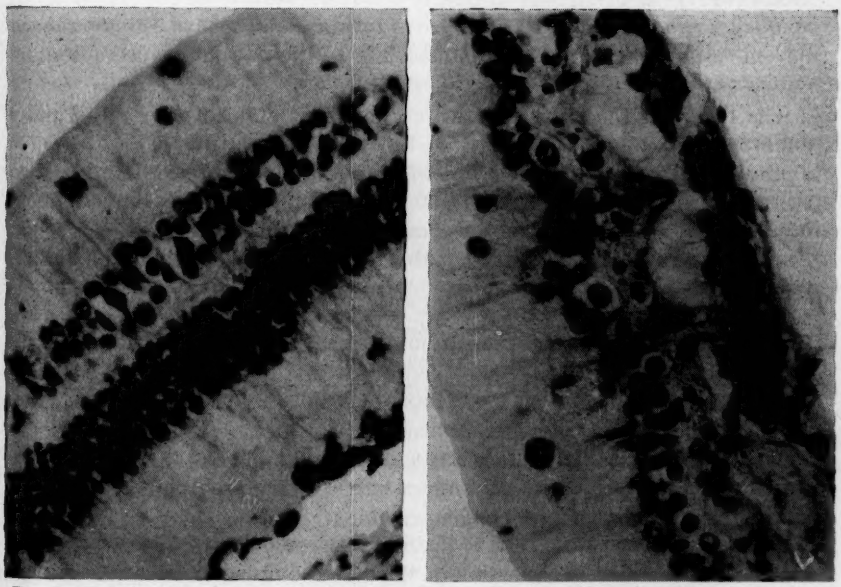


FIG. 2.—Rabbit retina 7 days after injection of 8 mg./kg. 1:9 di(*p*-aminophenoxy) nonane.
(*a*) Retina away from periphery. The cells of the pigment epithelium are swollen and disrupted. There are only minor changes in the visual cells.
(*b*) Retina towards periphery. There is loss of the visual cell layer; the pigment epithelium is swollen and disorganized. H and E ×400.

Discussion

The results recorded bring the new group of schistosomicidal drugs into line with the other agents that give retinal damage in the rabbit on a single intravenous injection: sodium iodate (Sorsby, 1941), sodium iodoacetate (Schubert and Bornschein, 1951; Noell, 1951), sodium bromoacetate (Lucas, Newhouse, and Davey, 1957), dithizone (Butturini, Grignolo, and Baroncelli, 1953), and cyanide and fluoride in combination (Sorsby and Nakajima, 1958). Edge and others (1956) failed to obtain a retinal lesion in the rabbit on oral administration of the primary amine they studied, and they considered that the rabbit, as well as several other animals, was not susceptible to this agent. As the present results show, the rabbit is readily susceptible when intravenous injections are used. In experimental degeneration of the retina induced by sodium iodate, sodium iodoacetate, sodium bromoacetate, dithizone, and cyanide and fluoride in combination, sub-lethal doses have to be employed. Table I suggests that the primary diaminodiphenoxyalkanes differ in this respect from these agents, for the doses producing retinal damage are well tolerated, and retinal damage appears to be produced by injections of quite small quantities.

The present study—like the parallel study by Goodwin, Richards, and Udall (1957)—is of interest in that it brings forward a substantial series of analogues producing retinal damage. Previous studies have not gone much beyond establishing sodium bromoacetate as the one analogue of sodium iodoacetate—and that with more limited efficacy.

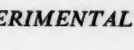
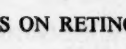
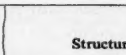
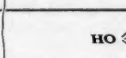
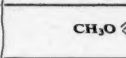
The fact that the most definite results were obtained with the primary amines in this series suggested that the noxious agent might be the *para*-aminophenoxy grouping. On this assumption, *p*-aminophenol and its two immediate analogues, *p*-anisidine and *p*-phenetidine, as also 4: aminophenol butyl ether containing four carbon chains and another substance with 7 carbon chains were tried experimentally. Table II (opposite) shows that, though sub-lethal doses were employed, no retinal damage was obtained ophthalmoscopically or histologically with any of these five agents. These negative findings are parallel to an observation recorded by Goodwin, Richards, and Udall on the hair of mice. They had noted that one of the toxic effects of the alkane derivatives on mice was loss of hair. No such effect was obtained by them when they used *p*-aminophenol.

It is not clear whether there is any significance in the fact that amongst the thirteen secondary and tertiary amines only the three substances with seven carbon chains gave positive results.

The observations recorded in Table III (overleaf) have not helped to elucidate the nature of the action of the diaminodiphenoxyalkanes. It will be seen that a modification in the central carbon chain as represented by the first agent listed (47C53) does not interfere with the retinotoxic effect of the primary alkanes. In contrast, the intact carbon chain and a

TABLE II

OBSERVATIONS ON RETINO-TOXIC EFFECTS OF *p*-AMINOPHENOL AND FOUR DERIVATIVES

Agent	Structural Formula	Lethal Dose (mg./kg.)	No. of Animals Used	Dose (mg./kg.)	No. of Injections	No. of Days Observed	Retinal Damage
p-aminophenol ..		770	3	(1) 1,170 (2) 970 (3) 1,700	8 3 3	20 13 10	None None None
p-anisidine ..		300	2	(1) 660 (2) 320	6 2	24 18	None None
p-phenetidine		100 (*a*) 150 (*b*) 300 (*c*) >50 (*d*)	1 1 2 1	180 250 (1) 100 (2) 290 110	2 2 1 2 2	1 24 3 27 12	None None None None None
4:aminophenol-butyl ether		50	1	50	2	10	None
11C54(d) Burroughs Wellcome ..		75	1	50	1	11	None

(*a*) In saline suspension. (*b*) In alcohol suspension.
(*c*) Dissolved in dilute HCl. (*d*) Purified by dissolving in dilute HCl and adding charcoal, and then filtered.

modification in the structure of the amino grouping, as represented by pentamidine, gives no retinal damage. The central carbon chain is also intact in the succeeding five agents and again there is no retinal damage. The last two observations in this Table show that it proved impossible to prevent the retinotoxic effect of one of the primary alkanes by a possible blocking effect of *p*-aminophenol, and by a possible 'detoxicating' effect of sodium thiosulphate.

Summary

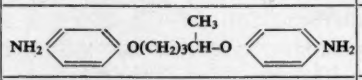
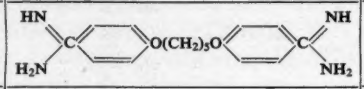
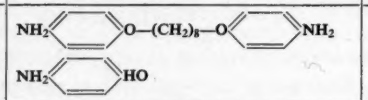
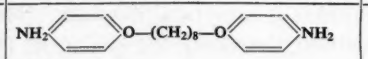
(1) Attention is drawn to the clinical and experimental findings by other observers on retinal damage produced by diaminodiphenoxyalkanes—agents that are being investigated for the treatment of schistosomiasis.

(2) Seven primary amines in the diphenoxyalkane series, two secondary methyl amines, seven tertiary methyl amines, and three tertiary ethyl amines, in all of which the amine was in the *para* position, as also one tertiary ortho-methyl amine, were tested in the rabbit by intravenous injection for their retinotoxic effect.

(3) Six of the seven primary amines gave marked degeneration of the visual cells and pigment epithelium after a single intravenous injection of quite small and well tolerated doses. Of the remaining agents, one secondary methyl amine, one tertiary methyl amine, and one tertiary ethyl amine—all with seven carbon chains—proved damaging to the retina, though the damage was relatively slight and obtained only with sublethal doses. The tertiary methyl amine that gave a retinal lesion—1:7 di(*p*-dimethylaminophenoxy) heptane—is the agent known to have produced damage in man.

TABLE III

FURTHER OBSERVATIONS BEARING ON THE MODE OF ACTION OF THE DIAMINODIPHENOXYALKANES

Agent	Structural Formula	Lethal Dose (mg./kg.)	No. of Animals Used	(mg./kg.) Dose	No. of Injections	No. of Days Observed	Retinal Damage
47C53 (Burroughs Wellcome) ..		?	1	22	1	18	++
Pentamidine* ..		$\bar{c}$. 20	1	20	1	42	—
Dodecamethylene diamine	$NH_2(CH_2)_{12}NH_2$	$\bar{c}$. 10	1	10	1	8	—
Dinitriles with central carbon chains	$CN—(CH_2)_3—CN$ $CN—(CH_2)_4—CN$ $CN—(CH_2)_{11}—CN$	$\bar{c}$. 150 ? 25 >100	1 1 1	328 (*a*) 25 (*b*) 469 (*c*)	6 2 7	55 5 60	— — —
Synthalin	$NH_2C:NH(CH_2)_{12}NH\,.\,C:NH_2$	5	2	3½ and 4	1	26 and 8	—
Primary diphenoxyalkane $n=8$ with *p*-aminophenol ..		14 770	1	5 and 160	1	18	++
Primary diphenoxyalkane $n=8$ .. with Sodium thiosulphate	 $Na_2S_2O_3$	14 ?	1	5 and 1,100	1	18	++

* Used as the isothionate salt.
(*b*) In two doses of 10 and 15 mg./kg.
(*a*) In six doses of 10, 15, 26, 37, 90, and 150 mg./kg.
(*c*) In seven doses of 10, 20, 36, 53, 90, 190, and 70 mg./kg.

(4) The possibility that the *p*-aminophenoxy grouping was responsible for the retinal damage was not borne out by trials with *para*-aminophenol and four of its derivatives with carbon chains.

(5) There is little to suggest that either a long carbon chain or the diphenoxy grouping is essential for a retinotoxic effect. In its context the amine grouping is probably important.

We wish to thank Dr. O. D. Standen and his colleagues, Dr. R. S. F. Hennessey, Dr. L. G. Goodwin, and Dr. V. Udall, of the Wellcome Laboratories of Tropical Medicine, for the considerable trouble they have taken in supplying us with some of the agents used in this investigation and for helpful discussions. We are likewise obliged to Mr. S. Ellingworth of Imperial Chemical Industries (Pharmaceuticals Division).

We are indebted to Messrs. May and Baker for a supply of 1:5 di(*p*-aminophenoxy) pentane. We are obliged to Dr. D. R. Lucas for the histological reports and to Mr. R. Harding for technical assistance.

REFERENCES

ASHTON, N. (1957). *J. Path. Bact.*, **74**, 103.
BUTTURINI, U., GRIGNOLO, A., and BARONCELLI, A. (1953). *G. clin. Med.*, **34**, 1253.
CHESTERMAN, W., and LEACH, E. H. (1956). *Quart. J. micro. Sci.*, **97**, 593.

COLLINS, F. D. (1954). *Biol. Rev.*, **29**, 453.
EDGE, N. D., MASON, D. F. J., WIEN, R., and ASHTON, N. (1956). *Nature* (*Lond.*), **178**, 806.
GOODWIN, L. G., RICHARDS, W. H. G., and UDALL, V. (1957). *Brit. J. Pharmacol.*, **12**, 468.
GRANT, W. M. (1956). Personal communication.
——— (1958). "Drug Intoxications and Chemical Injuries", *in* "Systemic Ophthalmology", ed. A. Sorsby. 2nd ed., Butterworth, London.
LUCAS, D. R., NEWHOUSE, J. P., and DAVEY, J. B. (1957). *Brit. J. Ophthal.*, **41**, 313.
NOELL, W. K. (1951), *J. cell. comp. Physiol.*, **37**, 283.
RAISON, C. G., and STANDEN, O. D. (1954). *Trans. roy. Soc. trop. Med. Hyg.*, **48**, 446.
——— ——— (1955). *Brit. J. Pharmacol.*, **10**, 191.
SCHUBERT, G., and BORNSCHEIN, J. (1951). *Experientia* (*Basel*), **7**, 461.
SORSBY, A. (1941). *Brit. J. Ophthal.*, **25**, 58
——— and NAKAJIMA, A. (1958). *Ibid.*, **42**, 558.
———, NEWHOUSE, J. P., and LUCAS, D. R. (1957). *Ibid.*, **41**, 309.

Brit. J. Ophthal. (1958) **42**, 572.

CASE NOTES

OCULAR RHINOSPORIDIOSIS SIMULATING A TUMOUR*

BY

K. D. SHARMA, J. B. SHRIVASTAV, AND S. AGARWAL

From the Department of Pathology and Bacteriology, Medical College, Jabalpur, M.P., India

RHINOSPORIDIOSIS is generally a local inflammatory condition of the anterior nares, and it was thought that other parts of the body enjoyed freedom from this infection, until in 1909 Kirkpatrick, cited by Tirumurti (1914) and by Purandare and Deoras (1953), reported a case of rhinosporidiosis of the conjunctiva. Elles (1941) reviewed 25 cases of ocular rhinosporidiosis reported in the literature, in 22 of which the lesion occurred in the conjunctiva and in three in the lacrimal sac. In a series of sixty cases reported by Allen and Dave (1936), four occurred in the conjunctiva. Purandare and Deoras (1953) reported 100 cases of rhinosporidiosis in Bombay, the conjunctiva being affected in three cases and the lacrimal sac in two cases. The following case of ocular rhinosporidiosis is reported because of its unusual manifestation.

Case Report

A man was admitted to the ophthalmic ward of the Medical College Hospital, Nagpur, with a large lobulated mass involving the whole of the right lower eyelid and to some extent hanging over the face. The mass measured roughly 8 cm. at its largest diameter and extended upwards so as entirely to cover the eyeball (Fig. 1). It was soft and doughy to the touch. The overlying skin was smooth, glistening, and stretched, but intact. The palpebral conjunctiva was normal. The cornea did not show any ulceration. Examination of the nose did not reveal any tumour mass. A piece was taken from the ocular mass and examined under the microscope.

FIG. 1.—Ocular mass involving whole of right lower eyelid and entirely covering the eyeball.

Pathological Report.—The skin showed acanthosis and pseudo-epitheliomatous hyperplasia. The dermis showed a large number of sporangia, varying from 50 to 300 microns in diameter (Fig. 2, opposite). The sporangium showed a double contoured chitinous envelope and contained a large number of spores. Some of the sporangia were seen in different stages of degeneration and some were empty. Several spores were seen lying free in the stroma. In some fields spores and empty envelopes of the sporangia were surrounded by dense inflammatory exudate and occasional foreign body giant cells (Fig. 3, opposite).

* Received for publication September 24, 1957.

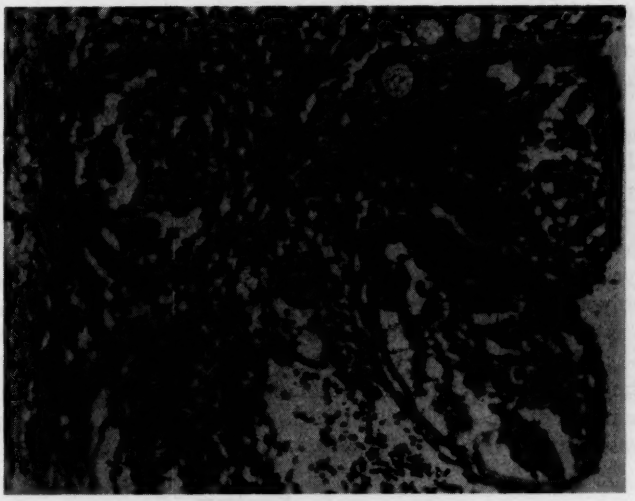


FIG. 2.—Photomicrograph showing sporangia in different stages of development. Haematoxylin and eosin, low-power magnification.

FIG. 3.—Photomicrograph showing spores and empty envelopes of sporangia surrounded by inflammatory exudate and foreign body giant cells. Haematoxylin and eosin, low-power magnification.

Discussion

Rhinosporidiosis was first described by Seeber (1900, 1912), who is cited by Ashworth (1923) and by Ash and Raum (1956). The disease is endemic in India, Ceylon, and Cochin-China, and several cases have been reported from the United States. The causative organism was originally considered to be a protozoon, but Ashworth (1923) proved it to be a fungus, and it has since been known as *Rhinosporidium seeberi*. The method of transmission

of the fungus is not known; it is believed that infection is acquired in bathing pools, but the fact that the infection occurs exclusively in males throws considerable doubt on this hypothesis.

The fungus produces polypoidal, soft, friable masses in the nasal mucosa, but the conjunctiva is occasionally involved, and less frequently the ear, pharynx, larynx, and genitalia. In the present case, no lesion was detected in the nares, whereas a solitary lesion confined to the lower eyelid was found. There was no ulceration of the conjunctiva. The route of transmission in this case had probably been direct through an abrasion in the skin of the eyelid or through the palpebral conjunctiva, leaving no trace behind. The polypoid lesion of the eyelid very closely simulated a neoplasm. This case was presented at the combined staff conference and the clinical diagnosis was "lymphangioma of the eyelid", until biopsy revealed the true nature of the lesion. It is emphasized that, in dealing with the differential diagnosis of tumours of the eyelid, rhinosporidiosis should always be kept in mind as a possibility in India.

Summary

A case is reported of ocular rhinosporidiosis simulating a neoplasm.

We wish to express our thanks to Dr. K. Chari, professor of ophthalmology, for the clinical data, and to Mr. Joshirao for the photograph.

REFERENCES

ALLEN, F. R. W. K., and DAVE, M. (1936). *Indian med. Gaz.*, **71**, 376.
ASH, J. E., and RAUM, M. (1956). "An Atlas of Otolaryngic Pathology", pp. 171–172. Washington.
ASHWORTH, J. H. (1923). *Trans. roy. Soc. Edinb.*, **53**, 301.
DUKE-ELDER, S. (1952). "Text-book of Ophthalmology", vol. 5, p. 4905. Kimpton, London.
ELLES, N. B. (1941). *Arch. Ophthal.* (Chicago), **25**, 969.
PURANDARE, N. M., and DEORAS, S. M. (1953). *Ind. J. med. Sci.*, **7**, 603.
SEEBER, G. R. (1900). Thesis, Univ. Nac. de Buenos Aires.
——— (1912). "*Rhinosporidium kinealyi* et *Rhinosporidium seeberi*, une question de priorité". Buenos Aires.
TIRUMURTI, T. S. (1914). *Practitioner*, **93**, 704.

Brit. J. Ophthal. (1958) **42**, 575.

BOOK REVIEWS

Systemic Ophthalmology. By ARNOLD SORSBY. Second edition, 1958. Pp. 682 and Index pp. 19, 277 figs, 24 c.p. Butterworth, London. (5 *guineas*)

The first edition of this book appeared in 1951; in view of its value it is not surprising that a second has now been found desirable. It covers a wide field wherein ophthalmology meets general medicine, surgery, obstetrics, dermatology, immunology, and neurology. The subject matter of the previous volume has been brought up to date and its general outline has been maintained, but two new chapters have been added, replacing old ones—on the nature of congenital malformations (Sorsby), and on gout (Savin)—and the authorship of other chapters has been changed. The book remains an excellent and authoritative guide to the wider aspects of ophthalmology and its general medical implications.

BOOKS RECEIVED

The following books will be reviewed in *Ophthalmic Literature*:

Clinical and Practical Ophthalmology (In German). Edited by W. ROHRSCHNEIDER. 1958. Pp. 398, 117 figs, bibl. Enke, Stuttgart. (D.M. 39·50; £3. 5*s*.).

Heterophoria (In Italian). By C. TOSELLI. 1957. Pp. 287, 28 figs. Rosenberg and Sellier, Turin, Italy. (£3. 19*s*. 6*d*.)

NOTES

FACULTY OF OPHTHALMOLOGISTS

Study Tour to France and Switzerland, 1958

Lyons.—The party was first welcomed to Professor Paufique's clinic at Lyons. The visit was of immense interest and excited admiration of all that was seen and heard. An operating session occupied the first morning, during which the party saw a keratectomy, a cataract extraction with trypsin, a ptosis operation, several lamellar grafts, the removal of a limbal dermoid from an infant, and division of an anterior synechia. Two other lists were also in progress in adjacent theatres.

A full programme was arranged for the rest of the week, including further operating sessions, out-patient clinics, ward rounds, and films and demonstrations in the orthoptic and glaucoma departments. On the last morning the party was royally entertained by the professor and his colleagues after the operating session, and in the evening their erstwhile hosts were their guests at dinner.

Geneva.—A two-day visit was then paid to Professor Franceschetti's clinic in Geneva, where a series of lectures, demonstrations, and operations had been planned to show every aspect of his work.

There was a talk on sodium versenate, a histological demonstration concerning diabetic retinopathy, an interesting demonstration of twins, a film of an orbital implant, demonstrations of applanation tonometry, electroretinography, and photo-coagulation, and a film on surgical treatment of the updrawn pupil. There was also a film of corneal grafting, a demonstration on genetics, a discussion between the professor and a dermatological colleague, Dr. U. Schnyder, about hyper- and dys-keratosis, a demonstration of the lamellar grafting donor-taking machine, and a visit to the laboratory where breeding experiments on heterochromia in cats are being conducted. On the social side, there was a delightful cocktail party given by Madame Franceschetti and a dinner with the Professor and his colleagues.

There seems no doubt that this tour was an outstanding success from every point of view. Innumerable new techniques were learned, immense interest was taken in the organization of the clinics and ophthalmic services in the two countries, and many good friends were made.

American Ophthalmological Society

The following officers have been elected for 1959:

President: Dr. Derrick Vail (Chicago).
Vice-President: Dr. Algernon B. Reese (New York).
Secretary-Treasurer: Dr. Maynard C. Wheeler (New York).
Editor: Dr. Gordon M. Bruce (New York).

Ophthalmological Society of Brazil

Officers, 1958–1959

President: Dr. Pedro Moacyr de Aguiar
Vice-President: Dr. Marcello Martins Ferreira
Secretary-General: Dr. Carlos Henrique Bessa
Treasurer: Dr. Renato Pereira Machado

OBITUARY

William Zentmayer

Readers of this Journal will be sad to learn of the death of Dr. William Zentmayer on March 18, 1958, at the advanced age of 93. Zentmayer was one of the great figures of a previous generation of American ophthalmology; even up to his death he maintained his interest in our specialty, serving on the Editorial Board of the *Archives of Ophthalmology*, which he had joined when it was started in 1929. In America his loss will be sincerely felt: and beyond America his many friends will regret the passing of yet another of the great figures who have contributed much to ophthalmological progress.